UNDERSTANDING HOW CLIENTS MAKE MEANING OF THEIR VARIANTS OF UNCERTAIN SIGNIFICANCE IN THE AGE OF MULTI-GENE PANEL TESTING FOR CANCER SUSCEPTIBILITY

by
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ABSTRACT

Background: Many clients who undergo genetic testing (GT) for cancer risk assessment receive variant of uncertain significance (VUS) result(s) whose association with cancer is unknown and lacks clinical utility. Clients' cognitive and affective perceptions (i.e. their interpretations) of uncertain genetic information often deviate from their memory of the information communicated by their genetic health care provider (GHP) (i.e. their recollections). This study describes clients' perceived uncertainties about their VUS result and differences between clients' recollections and interpretations of genetic risk information.

Methods: Participants included adults with one or more VUS result(s) in a cancer susceptibility gene identified by GT. Participants completed a survey of quantitative scales measuring their perceived uncertainties about their GT result and their recollections, thoughts, and feelings about (1) the pathogenicity of their variant result; (2) their risk for developing cancer and (3) the likelihood that cancer is hereditable in their family. Summary statistics and bivariate analysis were used to describe the outcomes of interest.

Results: Among the 68 participants, the majority were female (93%), Caucasian (97%), and college educated (59%). Most participants (82%) had multi-gene panel testing that identified one VUS (85%) on average 1.7 years ± 2.1 prior to study enrollment. Participants reported high perceptions of certainty about their GT result with a mean of 3.97 ± 0.81 out of 5 and a median of 4.06. Although thirty-six participants (60%) recalled a VUS result, only 30 (50%) felt their variant was a VUS. Furthermore, many participants thought (35%) and felt (43%) differently about their variant's pathogenicity

than their recollection. Compared to their recollection, participants perceived significantly higher cancer risks and hereditary likelihoods ($p<0.01$). Moreover, most participants (≥73.3%) reported that their GT result had influenced their risk perceptions. **Conclusion:** Regardless of their recollection, most participants perceived themselves and their families to be at greater risk for cancer suggesting false alarm. It is concerning that most clients do not seem to appreciate the inherent uncertainties about their result and that they are using their VUS result to inform their cancer risk perceptions. These findings have significant implications for what providers should address when conveying VUS results.

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BACKGROUND

A variant of uncertain significance (VUS) is a genetic mutation whose association with disease risk is unknown (National Library of Medicine, 2016). Existing information about a VUS result lacks reliability, credibility, or adequacy to classify the sequence change either as a normal variation or a disease-causing mutation and is therefore an inherently ambiguous test result (Han, Klein & Arora, 2011). The VUS result presents challenges to clinicians as they are left to make interpretations and medical management recommendations without clear or sufficient information. Currently there are no evidence-based guidelines describing how to manage patients who receive a VUS result and how or whether these results should be communicated to patients. Due to this lack of evidence, the National Clinical Cancer Network (NCCN) guidelines recommend that risk evaluation and management of individuals with a VUS in a cancer susceptibility gene should rely on empiric evidence based on the individual and family risk factors rather than the individual's genetic status (NCCN, 2016). Individualized management may include increased surveillance as well as other interventions, such as surgery or chemoprevention based on family history rather than the VUS result.

Unfortunately, recent research has suggested that clinicians and individuals receiving a VUS may over-interpret the meaning of the result and use it to inform management (Plon et al., 2011; Vos et al., 2012). It has been argued within the context of research that investigators should consider returning a genetic test result when the associated risk for disease is high and has significant implications for clinical utility (e.g. reproductive implications, preventative screening etc.) (Bookman et al., 2006). However, due to its inherent uncertainty the VUS result lacks immediate clinical utility. These

challenges have led genetics experts such as Dr. Mary-Claire King, the discoverer of the *BRCA1* breast and ovarian cancer susceptibility gene, to recommend that genetic laboratories refrain from reporting VUS results in the context of population screening for *BRCA1* and *BRCA2*. Dr. King maintains, "Our goal is to make the lives of oncologists more straightforward, not muddier. That means getting rid of the problem of variants of unknown significance, which were invented in the course of commercial activity and have run amok since, wreaking havoc for patients and despair for providers who need to give patients clear information." (Helwick, 2015). Still others argue that returning VUS results gives patients the opportunity to take part in family segregation studies that can aid in reclassifying the variant as a disease causing or benign variation (Garrett et al., 2016). The potential benefits and harms of disclosing VUS results remain poorly defined, and few studies have explored how individuals attribute personal meaning to their result. This study explores how individuals who receive a VUS result perceive uncertainty related to their result and how this uncertainty relates to their thoughts and feelings about the pathogenicity of their result, their personal cancer risks and the hereditary nature of cancer in their family.

Objective and Specific Aims

The purpose of this study was to describe relationships between the clients' perception of uncertainty related to their variant of uncertain significance (VUS) result and their recollection and interpretation of the genetic information communicated by their GHP at the time of result disclosure. Informed by Vos' perception model of genetic counseling (2011), outcomes of interest include perceptions of the genetic risk information sub-divided into six variables that include recollections and interpretations of

(1) the pathogenicity of the VUS result (2) cancer risks and (3) hereditary likelihood. Recollections refer to the clients' memory of the information communicated by the GHP. Interpretations refer to the clients' thoughts and feelings about this information regardless of what they recall was communicated by their GHP. Thus, interpretations capture how individuals give meaning to the recalled information by selecting, weighing, and evaluating the information as a meaning-based approach to coping with the uncertainty.

First, this study seeks to explore how individuals who receive a VUS result in a cancer susceptibility gene perceive uncertainty related to their result. Additionally, this study seeks to describe whether discrepancies between client recall and interpretation of genetic risk information (including pathogenicity of their variant result, cancer risks, and hereditary likelihood) are associated with perceptions of uncertainty related to their VUS result.

Aim 1: To describe how clients who receive a VUS result perceive uncertainty related to their result.

Aim 2: To examine the relationship between perceived uncertainty and interpretations among individuals with a VUS result.

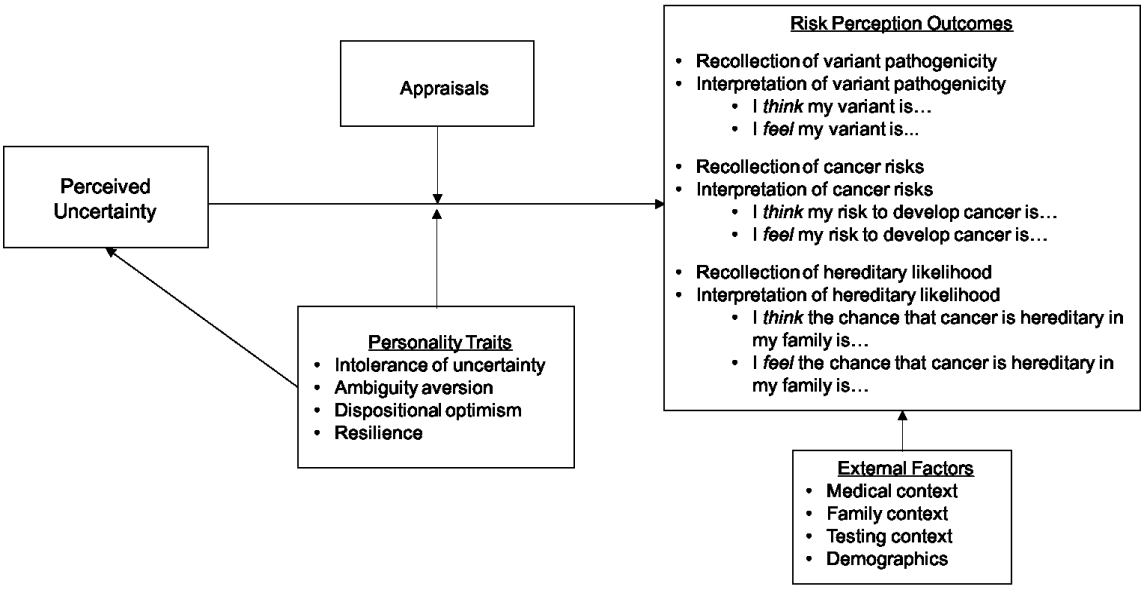
Aim 3: To assess whether perceptions of uncertainty and differences between recollections and interpretations are correlated with participant's personality traits of optimism, resilience, intolerance of uncertainty and ambiguity aversion.

Conceptual Framework

The conceptual framework (Figure 1) for this study draws from Mishel's theory of perceived uncertainty in illness (1988), Lazarus & Folkman's transactional model of stress and coping (1984), and Vos's perception model of genetic counseling (Vos et al.,

2011). Theories and models related to the concepts in this framework will be briefly described in this section and then research related to the relationships between these concepts will be highlighted in the following sections.

Figure 1: Proposed Conceptual Framework



The process of making meaning of a stressor or health threat is dynamic and is influenced by personal and environmental characteristics as well as the appraisals made of the threat (Park and Folkman, 1997). The Transactional Model of Stress and Coping (TMSC) posits that when faced with the stress of receiving an uncertain genetic test result an individual evaluates the personal significance of what is happening (primary appraisal) and what can be done about the result (secondary appraisal). As circumstances and an individual's values, beliefs, and goals (global meaning) change over time so will their appraisal, coping, and adaptation to the stressful event. Thus, appraisal and coping are not stable states but rather ever changing and influenced by dispositional personality traits as well as changes in the health threat and global meanings. Mishel's Perceived Uncertainty

in Illness Theory is like the TMSC in that it theorizes that cognitive appraisals of health threats occur prior to coping. According to the theory uncertainty is neither a desired nor unwanted state until the implications of uncertainty are determined.

This study's conceptual framework is also informed by Vos' (2011) perception model of genetic counseling (refer to page 16 for discussion). Measurement of recollections and interpretations of genetic information communicated as part of GCRA are key intermediary outcomes because they have been shown to better predict psychological, medical, and quality of life outcomes than the objective information communicated by genetic counselors (Vos et al., 2012). Outcomes in our model include recollections and interpretations of the genetic risk information that have been shown to predict downstream behavioral and psychological outcomes not measured in this study.

Unlike in Vos' perception model, interpretations in this study include both cognitive and affective perceptions of vulnerability when assessing perceived risk. This is informed by evidence that risk perceptions themselves can be both cognitive (i.e. thinking you are at risk) and affective (i.e. feeling you are at risk). Recent studies among diabetic and cancer populations have suggested that affective risk perceptions or affective states about risk - such as how worried, anxious or fearful a person is about developing cancer - may be better predictors of psychological and behavioral outcomes than traditional cognitive perceptions of risk (Portnoy et al., 2013; Janssen et al., 2012). Based on this evidence, our model incorporates individual's cognitive and affective interpretations of their genetic risk information separately.

In our model, the stressor or health threat is defined as receiving a VUS result. Informed by Mishel's theoretical framework, perceived uncertainty is measured as a

neutral construct while their appraisal indicates the relevance of the uncertainty to the individual. Similar to Mishel's framework, perception of uncertainties related to the VUS result is implicated as a predictor of how individuals will cope with their uncertainty. Meaning-based coping in this study is measured by the level at which the individual interprets their genetic information as being different than what they recall being communicated by their genetic healthcare provider, as informed by Vos' perception model of genetic counseling. Furthermore, based on the TMSC our model proposes that this process of making meaning of uncertainty related to a VUS result is influenced by the individual's appraisal of the VUS result and by their dispositional personality traits. We plan to assess the influence of these factors via moderation while holding constant other environmental characteristics that may influence the coping process.

Genetic Testing for Cancer Susceptibility Posited

Although all cancers develop as a result of mutations, only 5-10% of cancers are believed to be hereditary in nature (NCCN, 2016). The identification of germline pathogenic variants in genes associated with a high probability of cancer such as *BRCA1*, *BRCA2*, and those associated with Lynch syndrome allows for interventions that can significantly reduce the likelihood of developing cancer, make available targeted therapies for the treatment of associated cancers, and improve overall survival (Robson et al., 2015). These benefits are less understood in more recently described cancer predisposition genes that are associated with a moderate to low cancer susceptibility.

With the tremendous advances in genomic technology the clinical availability of genetic tests for hereditary cancer susceptibility is constantly expanding and has pushed cancer genetics providers to move beyond a well-established single gene paradigm. A

recent study of 603 genetic variants identified through clinical genetic testing for inherited cancer susceptibility, showed that a substantial proportion (37%) were classified as a VUS. Furthermore, early adopters of multi-gene panel testing for cancer susceptibility have shown that a substantial proportion of multi-gene panel tests identify a VUS in more than one gene with significant inter-panel variability (Kurian et al., 2014; LaDuca et al., 2014). VUS results are more common in a multi-gene panel approach both because of the sheer number of genes tested and the limited characterization of some genes. Clinically available multi-gene panel tests for hereditary cancer susceptibility include anywhere from 5 to 112 genes (GeneTests, 2016) and range between having a few high-risk genes focused on a specific organ (e.g. breast or colon) to those including all genes associated with tumor development in any organ system. For this reason, the probability of receiving a VUS result varies greatly by which test is selected. All existing research has exclusively examined how individuals make meaning of a VUS result in genes that are related to their personal and/or family history of cancer and in highly penetrant genes that if pathogenic would have clear clinical actionability. There is no evidence related to how this work may apply to genes conferring a low to moderate risk or confer a cancer risk that is discordant with the individual's personal or family history of cancer (Robson et al., 2015).

Uncertainty

Uncertainty is a multi-domain construct that is relevant across virtually all aspects of health and illness. Although researchers across many disciplines have explored the concept of uncertainty, the term has few explicit definitions. Han describes uncertainty as the "subjective perception of ignorance" that implies a conscious awareness of one's lack

of knowledge (Han et al., 2011). Babrow et al. (2000) posit that uncertainty arises when situations are ambiguous, complex, unpredictable, or probabilistic or when information is unavailable or inconsistent. Historically, literature regarding the conceptualization of uncertainty had failed to converge around a single model. However, Han and colleagues recently proposed an integrative taxonomy that categorizes uncertainty related to its sources, issues, and locus (Han et al., 2011). In this model, possible sources of uncertainty include probability, ambiguity, and complexity. Probability refers to the indeterminacy of future outcomes, ambiguity refers to the lack of reliability, credibility, or adequacy of information and complexity refers to the features of information that make it difficult to understand such as multiplicity of risks. Although ambiguity is at the core of a VUS result, recipients of a VUS may perceive uncertainty from all three sources. Under this framework, issues related to uncertainty may be scientific (data-centered), practical (system-centered), or personal (patient-centered). Finally, the locus of uncertainty pertains to whether the uncertainty is experienced by the patient, provider, or both.

Personal uncertainties involve those related to the psychosocial and existential issues that are important to the individual, including the personal meaning of illness or health information. Personal uncertainties may be strong determinants of reactions and behaviors by patients in response to uncertain information. Several qualitative studies have described personal uncertainties related to uncertain genetic test results. In one recent qualitative analysis of 20 individuals identified to have a VUS in a Lynch syndrome gene, participants described personal uncertainties related to whether their result meant they had Lynch syndrome, the meaning of the result for their future cancer

risks, and their family members' cancer risks (Solomon, 2013). This study also identified affective responses to receiving a VUS result including disappointment, frustration, sadness, and relief. These results are similar to another qualitative analysis exploring perception of uncertainties related to genome sequencing (Biesecker et al., 2014). In this study participants described personal uncertainties regarding how to feel about genetic information and whether the results and researchers can be trusted. Responses from this study led to the development of a reliable and valid scale aimed at measuring personal uncertainties related to genome sequencing in three domains; clinical, affective, and evaluative (Biesecker et al., 2016). This study seeks to expand upon this research by quantitatively measuring personal uncertainties related to a VUS result and qualitatively exploring additional uncertainties that may be unique to individuals receiving a VUS result in a cancer susceptibility gene through multi-gene panel testing.

Personality Traits and Uncertainty

Research has shown that some individuals interpret uncertain genetic test results as threatening information potentially leading to 'false alarm', while some interpret these kinds of results as an opportunity to believe that they do not carry a genetic predisposition for disease, potentially leading to 'false reassurance'. Studies have not yet identified what distinguishes these individuals from each other and the extent to which personality traits affect the appraisal and interpretation of medical uncertainty. Understanding how personality traits such as intolerance for uncertainty, ambiguity aversion, optimism, and resilience contribute to these discrepancies can better inform counseling practice by allowing clinicians to tailor interventions aimed at helping clients make meaning of uncertain genetic results.

Intolerance for Uncertainty

Research suggests that some individuals have a dispositional tendency toward more negative reactions when faced with uncertainty than others that is referred to as intolerance of uncertainty (IU) (Carleton et al., 2007). Individuals with relatively higher IU have been shown to exhibit a variety of cognitive, emotional, and behavioral reactions to uncertain information. For instance, IU has been well established as a key factor in predicting worry, and may be a predisposing or exacerbating factor across anxiety and major depressive disorders (Einstein, 2014). Furthermore, IU has been demonstrated to predispose individuals to approach uncertain situations in an inflexible and negative manner (Koerner and Dugas, 2008).

A small body of research has examined relationships between IU and perceived uncertainty related to genetic information. In a recent study of 494 asymptomatic adults undergoing genome sequencing, those who perceived high uncertainty were less likely to perceive positive health benefits of genome sequencing results only when the individual also had high IU (Taber et al., 2015). Additionally, in a study of 64 breast cancer survivors who received uncertain genetic results in *BRCA1/2*, those who had high IU and perceived their risk to develop another cancer to be high experienced the highest levels of distress a month after disclosure (O'Neill et al., 2006). These results suggest that those who are averse to uncertainty may be motivated to interpret the genetic information as differing from what was communicated by their genetic provider and to appraise their result as more threatening.

Ambiguity Aversion

Ambiguity aversion (AA) is a phenomenon characterized by pessimistic appraisals of ambiguous risks and choice options and subsequent avoidance of decision-making (Ellsberg, 1961). The characteristic that distinguishes AA from IU is that it specifically assesses negative reactions to ambiguous information rather than uncertain information that can be probabilistic, ambiguous, or complex. A recent survey of 1,074 adults found that individuals with high AA were more likely to perceive harms related to cancer screening and had greater ambivalence about the screening measures (Han et al., 2014). These results are in line with studies by Taber et al. (2015) that showed that higher levels of AA were correlated with lower intentions to learn genome sequencing results and Biesecker et al. (2016) that showed those who were more ambiguity averse had lower perceptions of uncertainty related to genome sequencing results. Although not directly tested in the latter study, authors hypothesized that those who are more ambiguity averse may be more motivated to mitigate the threat of uncertainty and thus report lower perceptions of uncertainty. Based on this hypothesis those who are ambiguity averse may also report lower perceptions of uncertainty related to a VUS result.

Resilience

Wagnild (2009) describes characteristics of resilience as perseverance or the act of persistence despite adversity or discouragement. Resilience has been found to be positively correlated with spiritual growth, health promoting lifestyle practices, and psychological wellbeing and negatively correlated with depression and anxiety (Wagnild, 2009). In a recent survey of 94 parents of children with undiagnosed diseases, resilience was associated with lower levels of perceived uncertainty and greater coping efficacy (Macnamara, 2014). However, in a study of 551 asymptomatic adults undergoing genome

sequencing higher perceptions of uncertainty were correlated with resilience (Biesecker et al., 2016). Discrepancy between these findings may at least partially be explained by inherent differences in the sources and issues of uncertainty related to raising a child with an undiagnosed condition versus related to the potential of future uncertain genetic test results. Since we plan to measure perceptions of uncertainty related to VUS results utilizing the same scale as the latter study we predict similar positive correlations between greater perceived uncertainty and resilience. In this study, we predict individuals who are more resilient will be better able to mitigate the threat of uncertainty and more apt to acknowledge the uncertainty related to the VUS result in their interpretations.

Optimism

Research has found that dispositional optimism, the tendency of an individual to expect positive outcomes in life, is protective against poor mental and physical health. Furthermore, research in genetic and non-genetic contexts has shown dispositional optimism to both directly affect levels of perceived uncertainty and to moderate its effects on other outcomes. Among a cohort of parents with children who have undiagnosed diseases, those who were more optimistic had lower levels of perceived uncertainty and felt more personal control over their child's condition (Madeo et al., 2013). Similarly, in a small quantitative study of 30 individuals scheduled to receive an implantable defibrillator, those who were more optimistic perceived less uncertainty related to the procedure (Carroll and Arthur, 2010). In Taber et al.'s study (2015) those with high perceived uncertainty expressed lower intention for learning non-medically actionable sequencing results only when they had low optimism. Collectively, these studies suggests that those with greater optimism may perceive less uncertainty related to

their VUS result and those with low optimism may form more pessimistic appraisals of uncertain genetic information. However, optimistic individuals who receive an uncertain genetic test result may alternatively be more likely to appraise the uncertainty positively and thus more likely to acknowledge the uncertainty related to their VUS result. We hypothesize that those with high optimism would be the least likely to over-interpret genetic risk information as threatening compared to their recollection of what was communicated by their genetic provider because they have an inherit tendency to expect positive outcomes.

Impact of Genetic Uncertainty

Much of the available research in the realm of genetic testing has suggested that receiving an uncertain genetic result is associated with psychological and behavioral consequences. Unfortunately, most of the literature on uncertain genetic test results resides within the study of Hereditary Breast and Ovarian Cancer (HBOC) associated with the *BRCA1/2* genes, and for this reason it can be assumed that all studies in this section have been conducted in BRCA populations unless otherwise specified. Potential uncertain DNA test results include (1) a VUS result and (2) results in which no variant is detected in the absence of a known familial mutation referred to as an uninformative result (UN). In contrast, certain DNA test results include (1) a pathogenic mutation (PM) and (2) results in which no variant is detected in the presence of a known familial mutation referred to as true negative (TN). Most studies regarding uncertain genetic results have focused on populations receiving UN results, which may not be applicable to the experiences of those with a VUS. Based on studies of UN results, many have described what Vos refers to as the "genetic uncertainty causes distress hypothesis",

which conjectures that disclosure of uncertain results cause more distress than those with certain results (Vos et al., 2008). Some research has provided evidence for this hypothesis indicating women who receive a certain TN result had lower levels of distress than women receiving an uncertain UN result (van Dijk et al., 2006). However, other studies showed reductions in acute distress for those with a VUS result while those with a PM result had similar or higher levels of distress (van Dijk et al., 2004).

Some researchers have also described the effects of uncertain DNA results on long-term distress. A retrospective exploratory analysis found that levels of distress and anxiety were comparable among individuals receiving uncertain and certain test results six months after disclosure and did not reach clinically significant levels (Claes et al., 2004). O'Neill et al. (2009) found that compared to those receiving an UN result, those receiving a VUS had higher genetic test distress one year after disclosure. Furthermore, in a retrospective case control study individuals with a VUS reported significantly less reduction in cancer distress than those with an UN result (Culver et al., 2013). These studies have presented mixed evidence in understanding the relationship between genetic uncertainty and psychological distress. One reason for this may be that these studies stratified individuals based on their DNA result and not on how they thought and felt about uncertainty related to their result. Mishel (1988) posits that anxiety related to uncertainty can turn into hope when individuals can reframe their experiences or accept the experiences as a natural consequence of life. Therefore, it may be that individuals who perceive uncertainty as an opportunity or see positive aspects to receiving a VUS result are less likely to experience distress related to the uncertainty. This study seeks to explore how individuals with uncertain genetic test results perceive uncertainty related to

their result, which could inform future research to better understand the relationship between genetic uncertainty and distress.

The impact of uncertain genetic test results on risk-related behaviors and medical management decisions has also been explored. Several studies have reported frequencies of prophylactic surgeries after receiving a VUS result that overlap with rates in PM cohorts raising concern that patients and providers may be over-attributing meaning to the uncertain genetic test result (Vos et al., 2008; Murray et al., 2011). A retrospective chart review of 107 VUS carriers found that 13 of 22 individuals who had risk-reducing oophorectomy reported that uncertainty related to their genetic test result influenced their decision (Murray et al., 2011). Similarly, a prospective study of 183 women with an uncertain UN result showed similar intentions for mammogram screening as those who received a certain PM result (van Dijk et al., 2005). These studies suggest clients' reactions to uncertainty related to their genetic result influence how they make decisions about their future medical management. Understanding how clients perceive uncertainties related to their result and how these perceptions influence their interpretations of genetic information could have important implications for how we communicate uncertainty and evaluate medical options with clients in the posttest counseling discussion.

Another commonly investigated outcome among individuals with uncertain genetic results is risk perception. Several studies have identified that a subset of individuals receiving uncertain UN results perceive their result as a certain TN, a phenomenon described as "false reassurance" (Bish et al., 2002; Claes et al., 2004). However, studies investigating those with an uncertain VUS show a greater variety in interpretation with some perceiving the result as a certain TN and some as a certain PM

(Ritcher et al., 2013;Vos et al., 2008). In studies specific to those with VUS results, risk perception has typically been operationalized as perception of cancer risk. A study of 36 VUS carriers found that 93% of participants perceived a change in their risk for cancer after disclosure of the VUS result, of which 32% of these perceived their risk for breast cancer as higher post disclosure (Ritcher et al., 2013). However, van Dijk et al (2004) found that perceptions of breast cancer risk did not change significantly post-disclosure among VUS carriers (van Dijk et al., 2004). Some studies seem to suggest that individuals have inaccurate perceptions of the meaning and significance of their uncertain DNA result on their health despite studies reporting high levels of comprehension of these results post-disclosure (van Dijk et al., 2004). Inconsistencies may be due to challenges with operationalization, as some individuals may be reporting on their recollection of what risk information was communicated while others are reporting on their own subjective meanings. Studies that have made this distinction between recall and interpretations of risk perception are discussed in the following section.

Differences in Recollection and Interpretation of Uncertain Genetic Information

Many individuals receiving uncertain DNA results differentiate between their recollection and interpretation of genetic information communicated by their genetic healthcare provider (Vos et al., 2008; Cypowyj et al., 2009; Solomon, 2013). In an exploratory qualitative study of 24 women with a VUS in *BRCA1/2* genes, most women in the study had a different interpretation than their recollection with 79% interpreting their VUS result as a PM and 21% as a TN (Vos et al., 2008). The authors proposed that when faced with uncertain genetic results individuals interpret the result with greater certainty as an adaptive way of coping with uncertain information (i.e. as a form of

meaning based coping). Given this hypothesis, perceptions of uncertainty and appraisals may influence a client's reinterpretation of genetic information communicated by their genetic healthcare provider. However, research has not explored how perception of personal uncertainties related to VUS results influence differences between recollection and interpretation of genetic information.

Responses from this qualitative study led to the development of a valid and reliable scale aimed at assessing an individual's recollections and interpretations of both their cancer-risks and hereditary-likelihood (Vos et al., 2011). This scale was utilized in a retrospective study of 206 patients who had undergone BRCA testing in which 76 received a VUS result, 77 an UN result, and 53 a PM result. In this study the authors collected information from patient visit summary letters to compare communicated genetic information to the individuals' recollections and interpretations. This study found that differences in recollections and interpretations of cancer risks and hereditary likelihood were greatest among those receiving a VUS result. Furthermore, the majority with a VUS overestimated their cancer risks and hereditary likelihood when compared to what their genetic counselor had communicated. This study supports the hypothesis that clients reinterpret genetic information as a form of meaning based coping. Furthermore, the observation that greater differences between recollection and interpretations were observed in the VUS group may be explained in part by the uncertainty related to the result and warrants further investigation.

Vos and colleagues went on to show that among the 76 participants in the VUS group, psychological outcomes, quality of life, BRCA-related stigma and vulnerability and medical outcomes were better predicted by the participants' interpreted cancer risks

and hereditary likelihoods than by the communicated information (Vos et al., 2012). These findings were confirmed in a small prospective study of 16 VUS carriers surveyed pretest and three months post-disclosure (Vos et al., 2012). In both studies, those who interpreted their risks as greater than what was communicated by their genetic healthcare provider had more worries, distress, and greater uptake in prophylactic surgeries. Collectively these findings support the experience of false alarm and suggest that individuals receiving a VUS may appraise the result as a danger leading to over-estimation of cancer risks and hereditary likelihood and radical management.

This body of research advances our understanding of how individuals react and make personal meaning of uncertain genetic results in HBOC genes. However, several limitations to the generalizability of these results exist. First, these results may not reflect how individuals recall and interpret uncertain results in other cancer predisposition syndromes. Second, participants in the reviewed research have a personal and/or family history of cancer that is concordant with the genes tested. However, in the reality of multi-gene panel testing, patients often receive testing for genes that are not concordant with their specific personal and family phenotype. It is unclear in these cases whether individuals will perceive cancer risks and hereditary likelihood as related to the types of cancers in their personal/family history or the types of cancers associated with the gene their VUS was identified in.

METHODS

Study Population

Men and women who had genetic testing that identified one or more VUS result(s) in a cancer susceptibility gene no less than one month prior to the time of

recruitment were eligible for the study. Individuals had to be enrolled in an inherited cancer registry in which they have given permission to be contacted for future research. Exclusion criteria included individuals who are less than 18 years old, are not able to read and write in English, have a known variant in a cancer susceptibility gene classified as pathogenic, polymorphism, likely benign, or benign and whose VUS result(s) had been reclassified. The sample size calculation indicated that 240 participants were needed to have 80% power to detect the effect of a key independent variable to explain a small-to-medium effect size of at least 3.3% of total variance in differences in interpretation.

Recruitment Strategies

Participants were recruited through pre-existing research registries at two NCI designated comprehensive cancer centers; Moffitt Cancer Center located in Tampa, FL and City of Hope located in Duarte, CA. Participants are largely recruited to the registry through high-risk genetics clinic. As part of registry enrollment participants agree to be contacted in the event of future research opportunities. The registry research coordinators extracted eligible cases according to the inclusion/exclusion criteria and assigned each case a unique password to be used as the identifier for this study. The research coordinators emailed the eligible potential participants the recruitment letter (Appendix A), which included their unique password and a link to the informed consent document (Appendix B) and survey (Appendix C). Potential participants who did not have an email address were mailed the recruitment letter.

Procedures

This study involved a one-time self-administered survey. Individuals interested in the study were instructed to either access the web-based survey through a secure website,

SurveyMonkey, or to contact the researcher for a paper version of the consent document and survey. The first page of the online survey included a link to the consent document. Potential participants had the opportunity to read the recruitment letter and consent document at their leisure from the privacy of their homes and decide whether to participate. Participants were instructed that they could withdraw from the study and could discontinue the survey at any time. Participants were not asked to provide any identifiable information on the survey.

If cancer registrants were interested in participating they completed three screening questions, checked a box and inputted their unique password indicating that they had read the consent document and voluntarily agreed to participate. If the potential participant did not agree with any of the three screening questions they were thanked for their interest and instructed to exit the survey. Potential participants could decline the survey by checking a box and inputting their unique password on the first page of the web survey. A second recruitment email/mailing was sent by the registry research coordinator to all potential participants who had not completed, been deemed ineligible or declined the survey within 3 weeks of the first contact. Upon closure of the survey, the registry research coordinator released select genetic test report and clinical information for those participants who completed the survey linked to their unique passwords. Survey responses were collected from August 28, 2016 through January 5, 2017. This study was approved by the Institutional Review Boards of the University of South Florida (Protocol number Pro00026887) and City of Hope Hospital (Protocol number# 16219). The study was determined to be exempt from NHGRI IRB approval by the NIH Office of Research Protections (#13319).

Study Design

This study used a cross-sectional survey research design. Validated instruments were used to assess perceived uncertainties related to their VUS result, intolerance for uncertainty, ambiguity aversion, resilience, and optimism. The scales used to measure recall and interpretations of the VUS pathogenicity, cancer risks, and cancer heritability were adapted from Vos' validated scales (Vos et al. 2012). The survey was piloted among collaborating researchers, genetics experts and laypersons. The survey took approximately 15-20 minutes to complete.

Study Instrument

The survey (Appendix C) included scales to measure (1) personal uncertainties related to their genetic test result; (2) recollections and interpretations of the variant pathogenicity, cancer risks, and hereditary likelihood; (3) the degree to which their genetic test result influenced their interpretations; (4) personality traits and (5) decisional regret.

The Perceptions of Uncertainties in Genome Sequencing (PUGS) Scale

The PUGS scale was used to measure participants' perceptions of certainty or uncertainty about their genetic test result. The PUGS was developed to assess anticipated personal uncertainties related to genome sequencing as informed by Han's conceptual taxonomy of uncertainty in health care (Han et al., 2011). The PUGS is an 8-item scale encompassing three domains; clinical (three items), affective (three items), and evaluative (2 items). An example of items in each domain are "what actions I need to take based on my test results" in clinical, "whether to be worried or concerned about my test results" in affective, and "whether my test results are accurate" in evaluative. For each item

participants rated their level of certainty or uncertainty regarding their genetic test result on a 5-point Likert scale from 1 (very uncertain) to 5 (very certain). Final summed and averaged uncertainty scores can range from 1-5 with higher scores indicating greater certainty. Preliminary psychometric evaluation of the PUGS scale has found it to be valid and reliable (Cronbach's $\alpha = 0.83$; Biesecker et al., 2016). An open-ended question was used to capture any additional ways that participants felt certain and/or uncertain about their genetic test result that were not captured by the PUGS scale.

To assess what Han and colleagues (2011) describe as the locus of uncertainty (i.e. whether uncertainty is experienced by the patient, provider, or both) participants completed the 5 items in the clinical and evaluative domains of the PUGS scale a second time rating their genetic counselor and/or physicians' level of certainty or uncertainty about their genetic test result. To adapt the scale for this purpose the heading was modified in a way that prompted participants to rate their genetic providers' level of uncertainty and the item "how my doctor may use my results to improve my health" was modified to "how they may use my results to improve my heath" as well as the item "whether I can trust my test results" was modified to "whether they can trust my test results". The additional items and scoring of the scale remained the same.

Recollections and Interpretations of Pathogenicity, Cancer Risks, and Hereditary Likelihood

The items used to measure recollections and interpretations were adapted from Vos et al. 2008 & Vos et al. 2012. Participants first answered three items regarding their recollection of what their genetic healthcare provider had communicated, regardless of their thoughts and feelings; (1) the classification of their genetic test result, (2) the chance

that they will develop cancer in the future, and (3) the chance that cancer is hereditary in their family. Subsequently, in the interpretation section of the survey participants answered the same three questions under the instruction that they describe their own thoughts and feelings regardless of what their genetic healthcare provider had communicated.

DNA Result Pathogenicity

Participants were first prompted to "think about the one variant that is most important or that you feel may mean the most for you" and then were asked to report how their genetic counselor or doctor had classified that variant by selecting 1 of the 5 standardized classification categories put forth by the American College of Medical Genetics (2015): benign, likely benign, uncertain significance, likely pathogenic, and pathogenic. A description of "benign", "uncertain significance", and "pathogenic" were provided. Subsequently, participants were prompted to think about the same variant and to complete the sentences "I *think* my variant is…" and "I *feel* my variant is…" using the same 5 classification categories.

General Cancer Risk Perception

Participants first rated their risk to develop cancer in the future according to their genetic counselor or doctor on a 7-point scale from 1 (extremely unlikely) to 7 (extremely likely). In the subsequent section they were asked to complete the sentences "I *think* my risk to develop cancer in the future is…" and "I *feel* my risk to develop cancer in the future is…" using the same 7-point scale. Two open-ended questions were used to capture what types of cancer participants thought and felt they were at risk of developing respectively. Finally, participants rated in two items how much their genetic test result

had influenced their thoughts and feelings about their risk to develop cancer in the future on a 7-point scale from 1 (not at all) to 7 (extremely). An open-ended question was used to collect the specific ways (if any) that their genetic test result had changed their cancer risk perceptions.

Hereditary Likelihood

Participants first rated the chance that cancer is passed down from generation to generation in their family according to their genetic counselor or doctor on a 7-point scale from 1 (extremely unlikely) to 7 (extremely likely). In the subsequent section, participants were asked to complete the sentences "I *think* the chance that cancer is passed down from generation to generation in my family is…" and "I *feel* the chance that cancer is passed down from generation to generation in my family is…" using the same 7-point scale. Two open-ended questions were used to capture what types of cancer participants thought and felt were passed down in their family from generation to generation respectively. Finally, participants rated in 2 items how much their genetic test result had influenced their thoughts and feelings about their risk to develop cancer in the future on a 7-point scale from 1 (not at all) to 7 (extremely). An open-ended question was used to collect the specific ways (if any) that their genetic test result had changed their perception of hereditary likelihood of cancer in their family.

Intolerance of uncertainty

General intolerance for uncertainty was measured using the 7-item Intolerance of Uncertainty Scale (Carleton, Norton, Asmundson, 2007; $\alpha = 0.80$), which assesses the extent to which individuals are comfortable with uncertain situations. Participants are asked to indicate how characteristic each of the 7 statements are for them on a 5-point

scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). Final summed and averaged scores can range from 1-5 with lower scores indicating a greater intolerance for uncertainty.

Dispositional optimism

Dispositional optimism was measured using the average of the sum of 3 items (1, 4, & 10) from the Life Orientation Test-Revised (LOT-R) scale (Scheier et al., 1994; α= 0.85). Items are scored on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Final summed and averaged scores can range from 1-5 with higher scores representing higher optimism.

Ambiguity aversion

Medical ambiguity aversion was measured using the 6-item Ambiguity Aversion in Medicine scale (AA-Med), which assesses an individual's aversion to medical tests or treatments that experts have conflicting opinions about (Han et al., 2009; α= 0.79). Items are scored on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Two items (4 & 5) are reverse scored and all 6 are summed and averaged. Higher scores indicate greater ambiguity aversion.

Resilience

Resilience was measured using the 10-item Connor-Davidson-Resilience Scale (CD-RISC) that assesses an individual's perceptions about their ability to recover from or adapt positively to difficult situations (Campbell-Sills & Stein 2007; α= 0.85). Items are scored on a 5-point scale ranging from 0 (never true) to 4 (always true). A total resilience score is calculated by summing the responses, and higher scores indicate higher resilience.

Decision Regret

The Decision Regret Scale was used to measure the extent to which participants regretted having had genetic testing. The Decision Regret Scale was developed to measure "distress or remorse after a (health care) decision" (Brehaut et al. 2003; α= 0.81). Respondents were asked to reflect on their decision to have genetic testing, and then asked to indicate the extent to which they agree or disagree with 5 items on a 5-point scale ranging from 1 (strongly agree) to 5 (strongly disagree). Two items are reverse scored (2 & 5) and all 5 are summed and averaged. Higher scores indicate greater regret.

Other covariates

Additional questions were included to account for other possible confounding variables associated with perception of uncertainties, recall and interpretations of DNA result pathogenicity, cancer risks, and hereditary likelihood. These include four yes or no questions assessing (1) whether the participant is the first person in their family to have genetic testing (2) whether they were aware of the possibility of uncertain test results prior to disclosure (3) whether they received a genetic counseling summary letter or test report and (4) whether they reviewed their letter or test report during the survey. Finally, to assess subjective comprehension respondents were asked to rate how well they feel that they understand their genetic test result on a 5-point scale ranging from 1 (not at all) to 5 (very good).

Registry Data

Select clinical and test report data was obtained from the research registry. Data provided by the research registry included: (1) self-reported cancer-related personal and family health information (i.e. types of cancers, ages at diagnosis, and relationship to the

participant); (2) self-reported demographics (i.e. gender, race/ethnicity, highest level of education, marital status, number of children, and sex of their children); and (3) information from the genetic test report (i.e. date of the test, whether the genetic test ordered was for a single gene or multi-gene panel and the name of the gene(s) in which a VUS was identified). The data obtained from the registry originated through prior self-reported questionnaires, a pedigree collected by a genetics health care provider, and the clinical genetic test report.

RESULTS

Recruitment

A total of 514 individuals were deemed eligible by the research coordinators at each participating institution and were approached for recruitment. There were 204 eligible participants at Moffitt Cancer Center and 310 eligible participants at City of Hope. The majority of participants were emailed the recruitment letter (81% of eligible cases at Moffitt and 59% of eligible cases at City of Hope). During the recruitment period from August 26, 2016 to January 5, 2017, 79 individuals started the online survey. No individuals declined the survey or were determined ineligible by the eligibility screening questions at the beginning of the survey. However, over the course of recruitment seven potential participants were deemed ineligible to participate by the registry and 12 potential participants were unable to be reached due to inaccurate contact information. The overall response rate was 16% (79/495).

All participants answered the survey electronically. Approximately 18% (n=14) of surveys were incomplete. In the majority of the incomplete surveys, participants did not answer beyond inputting their unique passwords, answering the eligibility questions, and

agreeing to participate. This suggests that these individuals likely felt that they were ineligible to participate after reading the criteria. Sixty-eight individuals (86% of respondents) completed at least some of the survey items. Participants were able to skip any question(s), therefore, the sample sizes for the scales vary, depending on each scales' missing values.

Table 1. Participant Recruitment (n=68)

Recruitment Source	N (%)	Response Rate
Moffitt Cancer Center	34 (50%)	16.7%
City of Hope	34 (50%)	11.7%

Patient Characteristics and Demographics

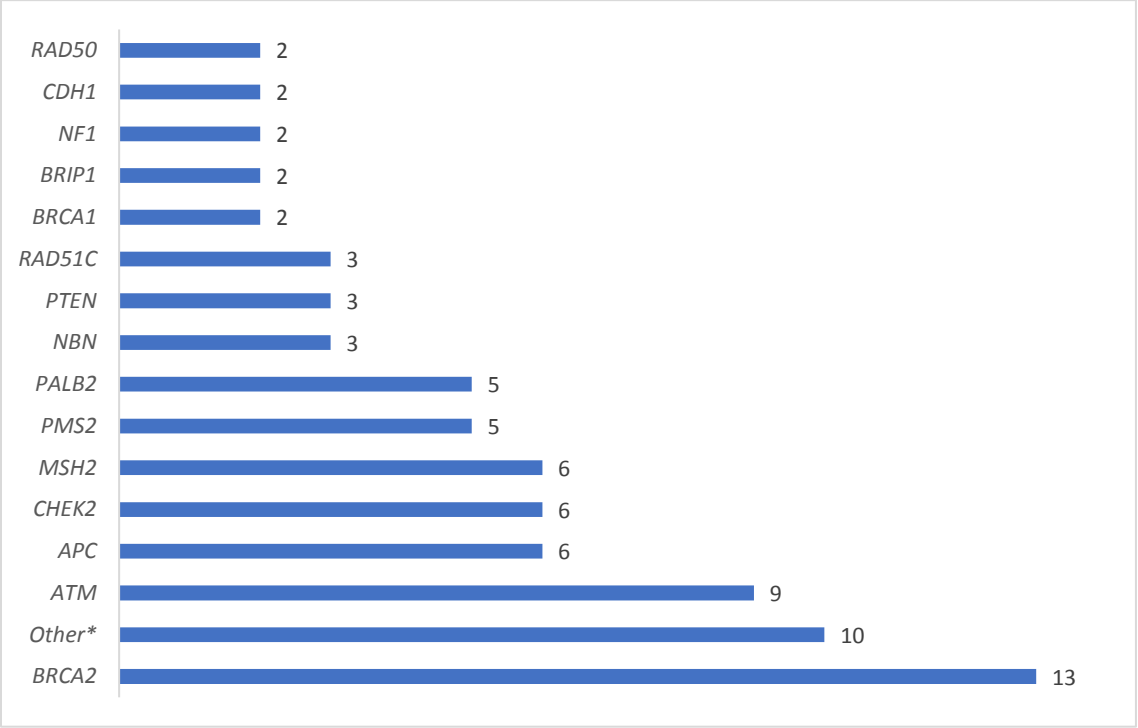
The mean age of participants in the study was 55.4 years (± 12.3). Participants were primarily female (93%), Caucasian (88%), married (71%), and college educated (59%). The majority of participants (82%) had a personal history of cancer of which the most common type was breast cancer (57%). All but two participants (97%) had a family history of cancer of which the most common type was breast cancer (66%). Table 2 summarizes the characteristics of the sample. Time since having genetic testing ranged between 4 months to 13 years with a mean time of 1.7 years ± 2.1. Most participants had multi-gene panel testing (84%) that identified one VUS in a cancer susceptibility gene (82%). Seventy-nine VUS results were identified in 26 genes among the sample. The most common gene reported to have a VUS was *BRCA2* (16%). The types of cancers associated with each gene were determined by reviewing National Comprehensive Cancer Network Guidelines and those reported in the clinical synopsis of the Online Mendelian Inheritance in Man (OMIM) catalog (Appendix D). These gene-cancer associations were used to determine which individuals had a VUS result in a gene that

was associated with their personal and/or family history of cancer. The names and frequency of genes harboring a VUS are described in Figure 2.

Table 2. Demographic Characteristics of Study Population (n=68)

	N	%		N	%
Gender			**Type of genetic test**		
Female	63	93	Single gene	11	16
Male	5	7	Multi-Gene Panel	57	84
Age			**Years since test**		
20-40	9	13	1 or less	39	57
41-60	35	52	2-5	27	40
61-80	23	34	> 5	2	3
Race			**First in family to have test**		
Caucasian	60	88	Yes	49	72
Other	8	12	No	16	24
Highest Education Level			**Number of VUS**		
≤ High School Graduate	7	10	1	56	82
Some College/Vocational	15	22	2	12	17
≥College Graduate	40	59	3	1	2
Marital Status			**Gene & Personal Cancer Hx**		
Married	48	71	Concordant	36	53
Other	16	24	Discordant	20	29
			No personal cancer hx	12	18
Ethnicity			**Gene & Family Cancer Hx**		
Hispanic	1	2	Concordant	45	66
Not Hispanic	33	49	Discordant	21	31
			No family cancer hx	2	3
Personal History of Cancer			**Family History of Cancer**		
Yes	56	82	Yes	66	97
No	12	18	No	2	3
Personal Cancer Types*			**Family Cancer Types***		
Breast	39	57	Breast	45	66
Skin	12	18	Lung	24	35
Colon	4	6	Colon	22	32
Ovarian	4	6	Prostate	21	31
Prostate	3	4	Skin	20	29
Other	12	18	Other	84	
Children			* Percentage does not equal 100% as participants may have had more than one type of cancer personally or in their family.		
Yes	53	78			
No	15	22			

Figure 2. Frequency of genes with a VUS (n=79)



* VUS genes that were present once in the sample population: *DIS3L2, MSH6, MUTYH, POLD1, RAD51D, SDHC, SMAD4, STK11, TSC2, VHL*

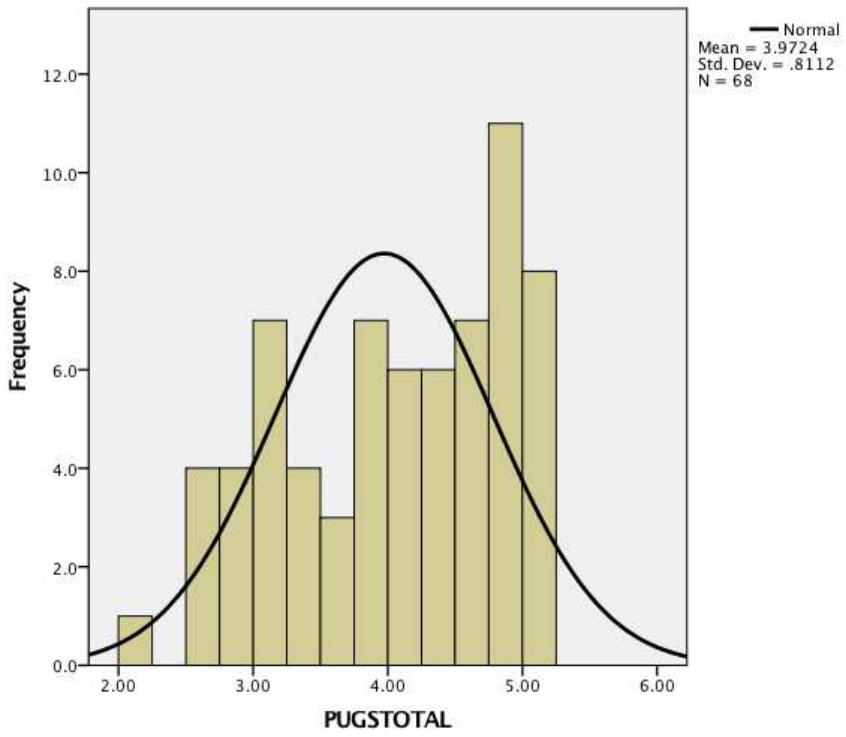
Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24.0 software. Frequencies were calculated for categorical variables and descriptive statistics including means, medians, ranges, and standard deviations were calculated for continuous variables. Associations between key variables were determined by t-tests and correlations. Bivariate analysis was used to explore the relationships between uncertainty and differences between recollections and cognitive and affective interpretations. Any analysis that resulted in a p-value ≤ 0.05 was considered statistically significant. Content analysis was conducted for open ended responses using the taxonomy of medical uncertainties in clinical genome sequencing (Han et al., 2017). Most responses were short and could be interpreted literally.

Perceptions of Uncertainties in Genome Sequencing (PUGS) Scale

The Personal Uncertainties in Genome Sequencing Scale (PUGS) was used to assess the participant's perceptions of uncertainty related to their genetic test result. Higher mean scores indicated greater certainty (possible range is 1-5). Overall, participants reported high levels of certainty about their genetic test result with a mean of 3.97 and a SD of 0.81. Scores ranged from 2.13 to 5 and the median was 4.06. The skewed distribution (Figure 3) suggests that the majority of participants perceive greater certainty than uncertainty about their VUS result. Descriptive statistics for the PUGS' three subscales are individually reported in the following sections.

Figure 3: Histogram of Total Personal Uncertainty Scores



Clinical Uncertainty

Uncertainty about the genetic test result's clinical utility was assessed with 3 items which asked about uncertainty related to how their result may affect their health, what actions they should take based on their result, and how their doctor will use their result to improve their health. Participant's clinical uncertainty scores ranged from 1 to 5, and the mean was 3.92 ± 1.06.

Affective Uncertainty

Affective uncertainty was assessed by three items which asked participants about uncertainty in whether they should be worried and concerned, alarmed, or if their results will disrupt their life. The scores for affective uncertainty ranged from 1 to 5, and the mean was 3.80 ± 1.12.

Evaluative Uncertainty

Uncertainty about the accuracy and trustworthiness of the genetic test result was assessed with 2 items. Participant's evaluative uncertainty scores ranged from 1.5 to 5, and the mean was 4.30 ± 0.81.

Additional Uncertainties

Participants were asked in an open-ended question to list any additional uncertainties they had that were not captured by the PUGS. As expected among a population of individuals who reported relatively high certainty on the PUGS, most participants (70.6%) either left the question blank or reported no additional uncertainties. Of those 20 who did report additional uncertainties, 3 participants simply mentioned that they had a variant of uncertain significance. The additional 17 responses were coded using Han and colleagues' taxonomy of medical uncertainties in clinical genome

sequencing. Guided by the taxonomy, participants conceptualized their additional uncertainties within two categories; ambiguity and scientific issues of uncertainty. Ten participants spoke to the ambiguity of their test result, with the majority (8/10) expressing uncertainty about whether there are genetic risk factors that were not identified by their testing and when they should have updated testing/information. Two participants mentioned uncertainty about conflicting interpretations of their genetic test result; in one case by two genetic laboratories and in another by two different health care providers. Eight participants spoke to the prognostic, diagnostic, and therapeutic uncertainties they had given their variant of uncertain significance result. Half (4/8) expressed uncertainty related to the implications of the result for family members and themselves. Another three participants spoke to uncertainty about their variant's association to cancer risk and one participant queried about whether there were treatments for her specific variant.

Table 3. Additional Uncertainties Associated with Test Result

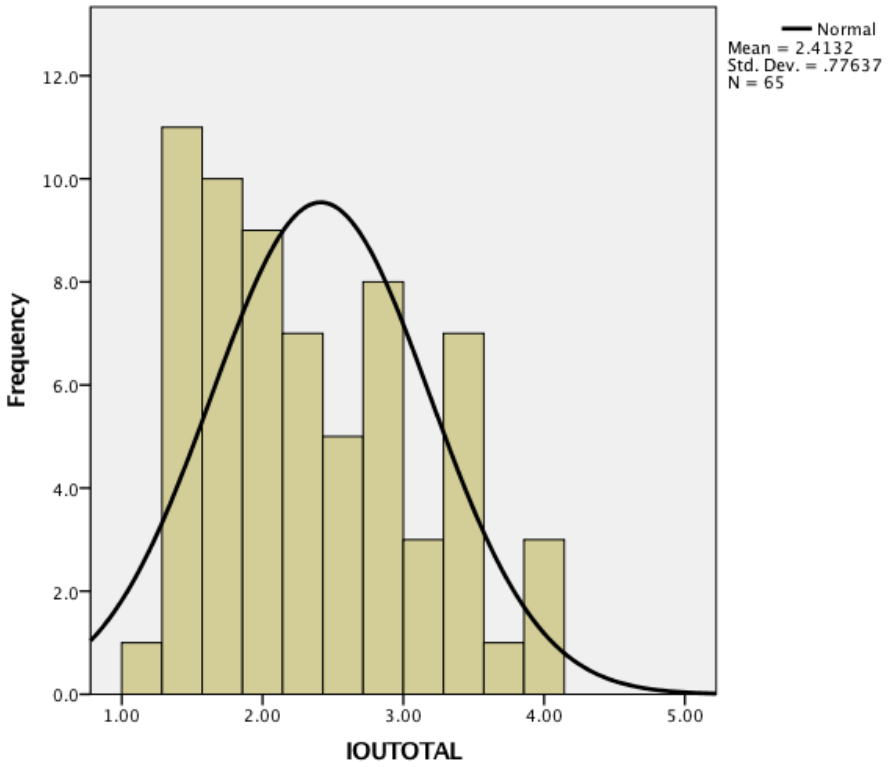
Sources/Issues of Uncertainty	Illustrative Quote
Ambiguity	
• Unmeasured factors (n=8)	"I am unsure if I have other abnormalities that may later be found to put me a greater risk." (Pt. 45)
	"How often I need to have new tests." (Pt. 64)
• Test misinterpretation (n=2)	"One test was of undetermined significance and my genetic doctor was not concerned about it. But later other doctors have attached meaning to it related to my cancer history." (Pt. 12)
Scientific	
• Prognostic (n=4)	"Whether the results have any implications for my children." (Pt. 54)
• Diagnostic (n=3)	"With a variant of unknown significance I am unsure if I have a higher risk for cancer that is genetic." (Pt. 45)
• Therapeutic (n=1)	"Any treatment for my specific gene mutation." (Pt. 58)

Personality Traits

Intolerance of Uncertainty

Participant's intolerance for uncertainty was measured using an abbreviated version of the Intolerance in Uncertainty Scale. Lower scores indicate individuals with greater intolerance for uncertainty (possible range is 1-5). Intolerance of uncertainty scores ranged from 1.14 to 4 and were slightly negatively skewed with a mean of 2.41 out of 5 and a SD of 0.77.

Figure 4: Histogram of Intolerance of Uncertainty Average Scores

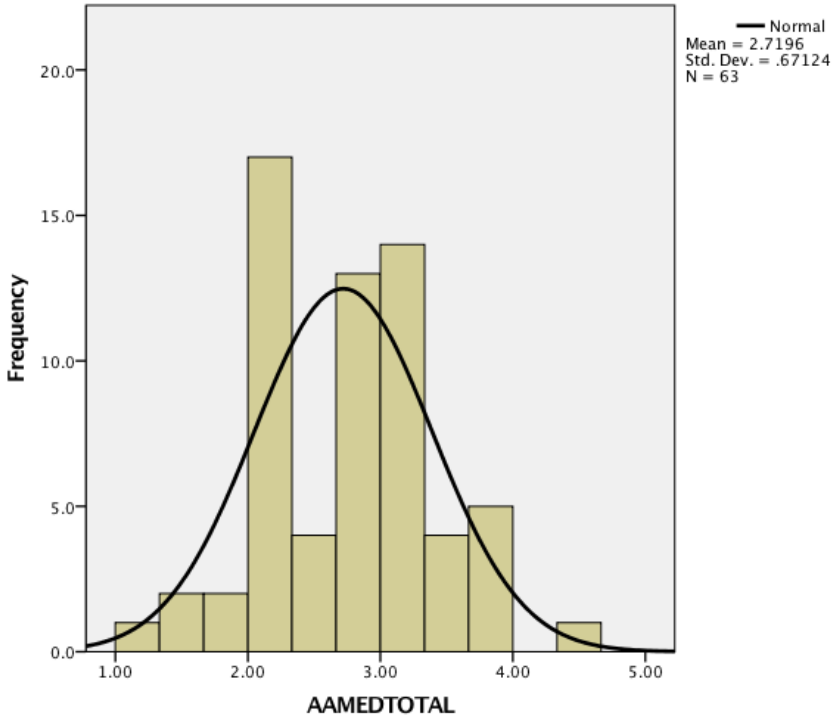


Ambiguity Aversion

The six item AA-MED scale was used to assess aversion to medical ambiguity. Higher scores indicate greater ambiguity aversion (possible range is 1-5). Ambiguity aversion scores ranged from 1.17 to 4.5, and were slightly positively skewed with a mean

of 2.72 out of 5 and a SD of 0.67. Ambiguity aversion and intolerance of uncertainty were moderately positively correlated (P_c=0.286 p=0.02). Thus, those who were less tolerant of uncertainty were more ambiguity averse.

Figure 5: Histogram of Ambiguity Aversion Average Scores

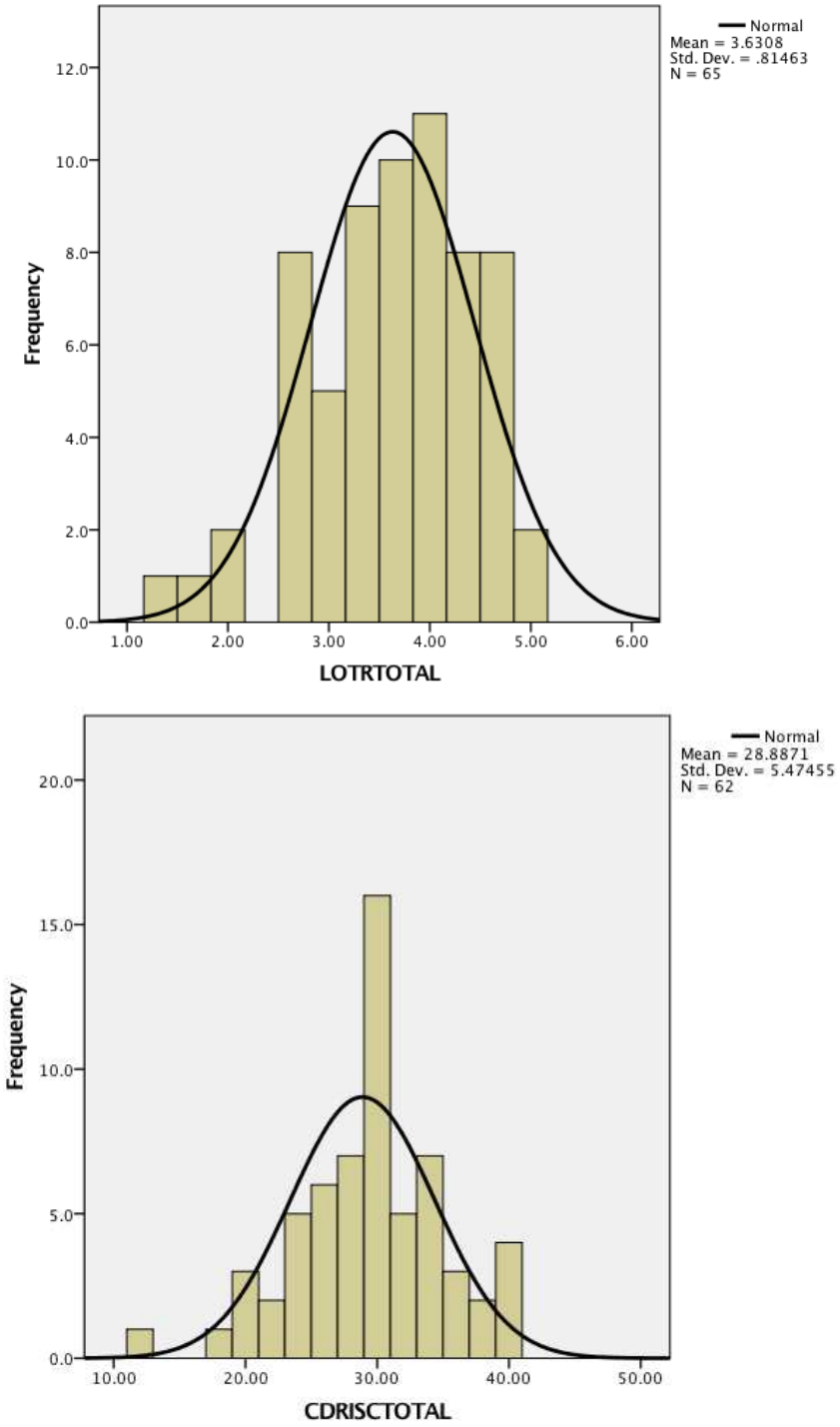


Optimism and Resilience

Three items from the LOT-R were used to assess dispositional optimism, where higher scores represented more optimistic individuals (possible range is 1-5). The 10 item Connor-Davidson-Resilience Scale (CD-RISC) was used to measure resilience, where higher scores represented greater resilience (possible range is 0-40). Respondents were relatively optimistic with a mean of 3.63 out of 5 and a SD of 0.81 (range of 1.33 to 5) and resilient with a mean of 28.89 out of 40 and a SD of 5.47 (range of 12 to 40). Resilience was highly correlated with optimism (P_c=0.483 p<0.001) and moderately

correlated to intolerance for uncertainty (P_c=-0.311 p=0.014). Thus, those with greater resilience were more optimistic and less tolerant of uncertainty.

Figure 6: Histograms of Optimism and Resilience Average Scores



Correlation of Personality Traits and Perceived Uncertainty

Bivariate analysis was performed to determine the strength and significance of predicted relationships regarding personality traits and perceptions of uncertainty based on the proposed conceptual framework (Figure 1). There was little evidence to guide hypotheses about how personality traits would be related to participant's perceptions of uncertainty. Therefore, we tested each trait against the overall perceived uncertainty as well as each domain of uncertainty measured by the PUGS. Overall perceptions of uncertainty were not correlated with intolerance of uncertainty, ambiguity aversion, optimism or resilience (Table 4). However, perceptions of evaluative uncertainty were correlated with ambiguity aversion (P_c=-0.34 p=0.006). Those who were more ambiguity averse had less certainty about the accuracy and trustworthiness of their test results.

Table 4. Pearson's Correlations among Uncertainty and Personality Traits

Resilience	Optimism	Ambiguity Aversion	Intolerance of Uncertainty	Evaluative Uncertainty	Affective Uncertainty	Clinical Uncertainty	Uncertainty Total	
							1.000 68	Uncertainty Total
						1.000 68	0.824** 68	Clinical Uncertainty
					1.000 68	0.466** 68	0.845** 68	Affective Uncertainty
				1.000 68	0.397** 68	0.374** 68	0.637** 68	Evaluative Uncertainty
			1.000 65	-0.032 65	-0.012 65	0.114 65	0.042 65	Intolerance of Uncertainty
		1.000 63	0.286* 63	-0.342** 63	-0.034 63	-0.013 63	-0.111 63	Ambiguity Aversion
	1.000 65	-0.112 63	-0.044 65	-0.005 65	0.038 65	0.187 65	0.111 65	Optimism
1.000 62	0.483** 62	-0.237 61	-0.311* 62	0.090 62	0.140 62	0.207 62	0.198 62	Resilience

*Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Perception of Genetic Health Care Provider's Uncertainty

Participants' perceptions of their genetic health care providers' uncertainty related to their genetic test result was assessed with the five items that make up the clinical and evaluative domains of the PUGS. Participants were prompted to rate their doctor or genetic counselors' level of uncertainty or certainty about their result. Thus, mean scores were calculated for the two measured subscales. In general, respondents tended to perceive their genetic health care provider as having high certainty about their genetic test result. However, their perceptions of their GHP's uncertainty were not statistically different than and they were highly correlated with their own perceptions (Table 5). This suggests that participants in this study likely perceive themselves and their GHP as sharing similar levels of certainty about their test result.

Table 5. Comparison of Perceptions of Personal and GHP Uncertainties (n=68)

Domains	Personal		GHP		t (p)	P_c
	Mean (SD)	Median	Mean (SD)	Median		
Clinical	3.92 (1.06)	4.33	3.98 (1.01)	4.00	0.60 (0.55)	0.745**
Affective	3.80 (1.12)	3.83	--	--	--	--
Evaluative	4.30 (0.81)	4.50	4.42 (0.74)	5.00	1.62 (0.11)	0.702**
Total	3.97 (0.81)	4.06	--	--	--	--

** Correlation is significant at the 0.01 level (2-tailed)

Recollections and Interpretations of Variant Pathogenicity, Cancer Risks, and Hereditary Likelihood

The second aim of this study was to explore participants' recollections, thoughts, and feelings about three pieces of information commonly communicated during cancer genetic counseling; variant pathogenicity, risk to develop cancer in the future, and likelihood that cancer is hereditary in their family. Frequencies were calculated for

variant pathogenicity variables and descriptive statistics were calculated for cancer risks and hereditary likelihood variables (Table 6).

The six key outcome variables were discrepancies between client recall and interpretation (i.e. thoughts and feelings) of three aspects of genetic risk information. Differences were calculated by subtracting the recollected score from the corresponding thoughts or feelings score. Positive scores represented those whose interpretation was greater than their recollected score (e.g. those who felt their future cancer risk was greater than their recollected risk). Negative differences represented those whose interpretation was less than their recollected risk (e.g. those who felt they are less at risk to develop cancer than their recollected risk). A score of zero represented those individuals who interpreted their risk to be the same as their recollected risk.

Table 6. Descriptive Statistics for Recollection, Thoughts, Feelings (n=60)

	Recollection	Thoughts	Feelings
Variant Pathogenicity (n, (%))			
Benign/ likely benign	20 (33.3)	19 (31.7)	18 (30)
Uncertain significance	36 (60)	32 (53.3)	30 (50)
Likely pathogenic/pathogenic	4 (6.7)	9 (15)	12 (20)
Cancer Risk (mean, (SD))	3.90 (1.25)	4.32 (1.36)	4.48 (1.32)
Hereditary Likelihood (mean, (SD))	3.97 (1.79)	4.67 (1.74)	4.73 (1.73)

Variant Pathogenicity

Recollection

Variant pathogenicity was measured on a 5-point scale that corresponded to the American College of Medical Genetics proposed variant classification categories. Thirty-six participants (60%) recalled that their genetic health care provider had classified their variant as uncertain significance, 20 (33.3%) as benign or likely benign, and 4 (6.7%) as pathogenic.

Thoughts

Thirty-two participants (53.3%) **thought** that their variant's classification was uncertain significance, 19 (31.7%) that it was benign or likely benign, and 9 (15%) that it was likely pathogenic or pathogenic. Most participants (65%; n=39) thought their variant's classification was the *same* as their recollection of what was communicated by their GHP. There was no difference in level of perceived uncertainty for those who thought differently about their test result compared to those who thought the same as their GHP (t=-0.75, df=58, p=0.45).

Feelings

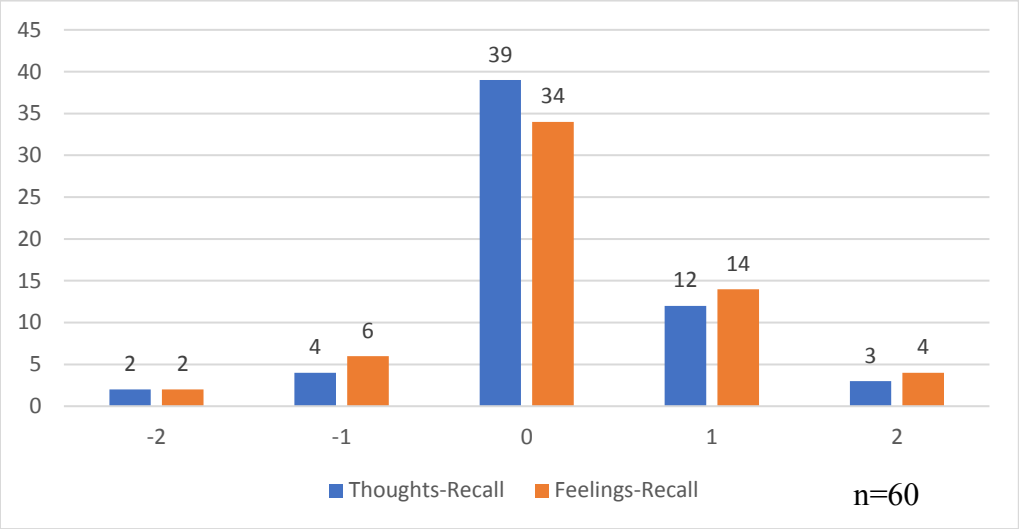
Thirty participants (50%) **felt** that their variant's classification was uncertain significance, 18 (30%) that it was benign or likely benign, and 12 (20%) that it was likely pathogenic or pathogenic. The majority of participants (56.7%; n=34) felt their variant's classification was the *same* as their memory of what was communicated by their GHP. There was no difference in level of perceived uncertainty for those who felt differently about their test result compared to those who felt the same as their GHP (t=-1.55, df=58, p=0.13).

Differences between recollection and interpretations

Respondents' recollection of their variant pathogenicity was subtracted from what they thought and what they felt their variant's pathogenicity was to assess discrepancies in recall and interpretations. Positive scores signified over-interpretation of their variant's pathogenicity compared to their recollection while negative scores signified under-interpretation (possible range is -4 to 4). Differences between thoughts and

recollection ranged from -2 to 2 and had a mean of 0.13 ± 0.72 while differences between feelings and recollection ranged from -2 to 2 and had a mean of 0.17 ± 0.81.

Figure 7: Histogram of Differences in Recollection and Interpretation Scores for Variant Pathogenicity



Cancer Risk

Recollection

Cancer risk perception was measured on a 7-point scale from 1 (extremely unlikely) to 7 (extremely likely). Overall, respondents recalled intermediate cancer risks of 3.9 out of 7 and a SD of 1.25.

Thoughts

Participants thought they were at an elevated risk to develop cancer: 4.32 out of 7 and a SD 1.36. Forty-eight participants (80%) reported that their genetic test result had influenced their thoughts about their risk to develop cancer, with 30% reporting that their perceptions were influenced very much or extremely by their result. Participants' cognitive cancer risk perceptions were not correlated with their overall perceived

uncertainty (P_c= -.127, p=0.33). However, perceptions of clinical uncertainty were correlated with their cognitive cancer risk perception (P_c=-0.27, p=0.04). Those who had less certainty (i.e. lower PUGS score) about how they would use their genetic test result clinically had higher cognitive cancer risk perceptions.

Feelings

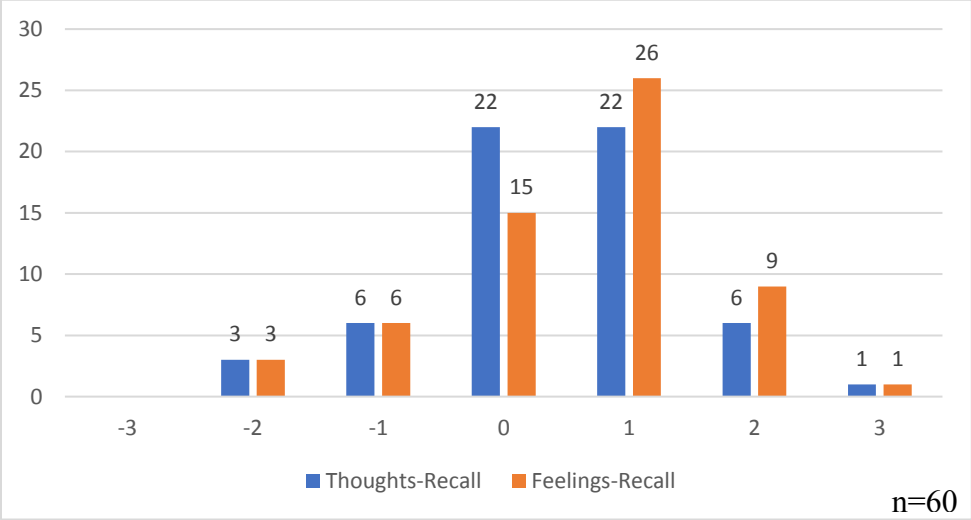
Participants felt that they were at an elevated risk to develop cancer of 4.48 out of 7 and a SD of 1.32. Forty-five participants (75%) reported that their genetic test result had influenced their feelings about their risk to develop cancer, with 30% reporting that their perceptions were influenced very much or extremely by their result. Participant's feelings about their risk to develop cancer were not significantly correlated with their overall perceived uncertainty about their genetic test result (P_c= -.0.246, p=0.06). However, their clinical uncertainty perceptions were more strongly correlated with their affective cancer risk perceptions than their cognitive cancer risk perceptions. Those who had higher perceived clinical uncertainty (i.e. lower PUGS score) felt they were at higher risk to develop cancer in the future (P_c= -.0.361, p=0.005).

Differences between recollection and interpretations

To assess discrepancies in recall and interpretations, respondents' recollection of their future cancer risk was subtracted from what they thought and what they felt their cancer risk was. Positive scores signified over-interpretation of their cancer risk perception compared to their recollection while negative scores signified under-interpretation (possible range is -6 to 6). Differences between thoughts and recollection ranged from -2 to 3 and had a mean of 0.42 ± 1.03 while differences between feelings and recollection ranged from -2 to 3 and had a mean of 0.58 ± 1.08. Most participants

(63.3% and 75%) thought and felt *differently* about their risk to develop cancer than what they recalled being communicated by their GHP. Moreover, participants thought and felt they were at a significantly higher risk to develop cancer in the future compared to their recollection (t=-3.13, p=0.003, df=59; t=-4.19, p<0.001, df=59).

Figure 8: Histogram of Differences in Recollection and Interpretation Scores for Cancer Risk



Hereditary Likelihood

Recollection

Perception of hereditary likelihood was measured on a 7-point scale from 1 (extremely unlikely) to 7 (extremely likely). Overall respondents recalled intermediate hereditary likelihoods of 3.97 out of 7 and a SD of 1.79.

Thoughts

Participants thought that there was a high chance that cancer was heritable in their family with a mean of 4.67 and a SD of 1.74. Forty-four participants (73.3%) reported that their genetic test result had influenced their thoughts about the hereditary likelihood in their family, with 30% reporting that their perceptions were influenced very much or

extremely. Participants thoughts about the hereditary likelihood in their family were not correlated with their perceived uncertainty about their genetic test result.

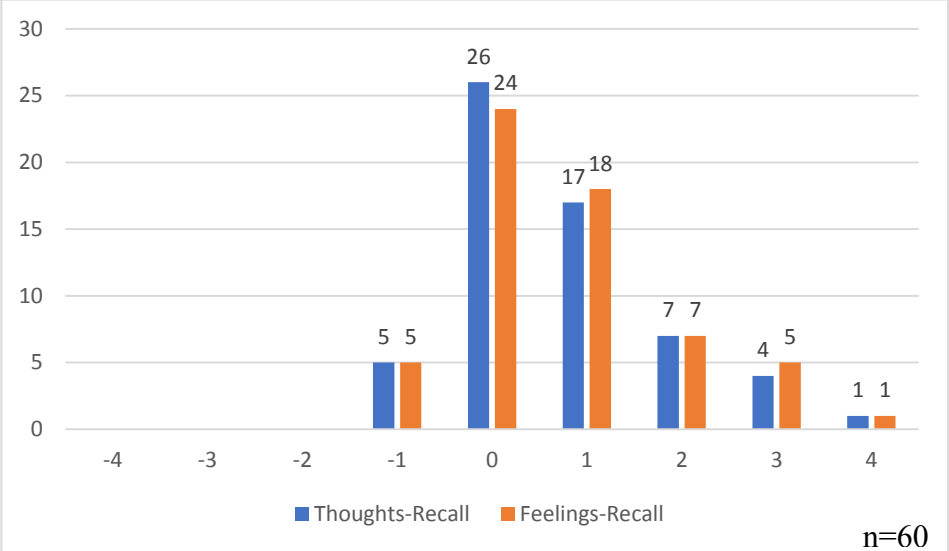
Feelings

Participants felt there was a relatively high likelihood that cancer was hereditary in their family with a mean of 4.73 and a SD of 1.73. Forty-four participants (73.3%) reported that their genetic test result had influenced their feelings about the hereditary likelihood in their family, with 30% reporting that their perceptions were influenced very much or extremely. Participants' feelings about the hereditary likelihood in their family were not correlated with their perceived uncertainty about their genetic test result.

Differences between recollection and interpretations

Participants' recollection of the likelihood that cancer was hereditary in their family was subtracted from what they thought and what they felt was their family's cancer hereditary likelihood. Positive scores signified over-interpretation of their cancer risk perception compared to their recollection while negative scores signified under-interpretation (possible range is -6 to 6). Differences between thoughts and recollection ranged from -1 to 4 and had a mean of 0.70 ± 1.11 while differences between feelings and recollection ranged from -1 to 4 and had a mean of 0.77 ± 1.14. Most participants (67.7% and 60%) reported thinking and feeling *differently* than their GHP about the chance that cancer was heritable in their family. Moreover, participants thought and felt a significantly higher chance that cancer was hereditary in their family compared to their recollected risk ($t=-4.89$, $p<0.001$, $df=59$; $t=-5.207$, $p<0.001$, $df=59$).

Figure 9: Histogram of Differences in Recollection and Interpretation Scores for Hereditary Likelihood



Subjective Comprehension, Expectations, and Decisional Regret

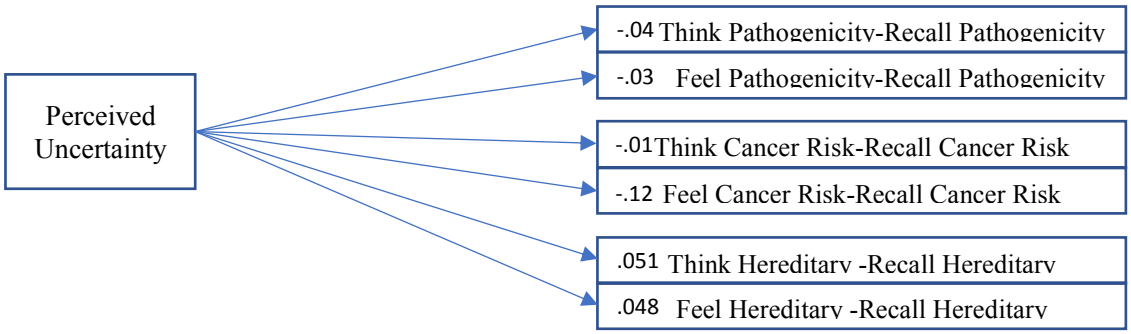
Respondents were relatively confident in their understanding of their genetic test result with a mean of 4.3 out of 5 and a SD of 0.67. Most participants (81.7%; n=49) reported that they knew of the possibility of an uncertain result prior to having genetic testing. Furthermore, respondents had relatively low regret about their decision to have genetic testing with a mean of 1.22 out of 5 and a SD of 0.61.

Correlation of Key Variables as Framed by the Conceptual Model

Using the conceptual model as a framework (Figure 1), bivariate analysis was performed to determine the strength of and significance of predicted relationships. We had little evidence to guide hypotheses about how perceived uncertainty would affect the key outcome variables. For this reason, perceived uncertainty was tested against each key outcome variable. Correlation analysis was used to determine which demographic and clinical characteristics were associated with key variables. Perceptions of uncertainty were not significantly correlated with any of the six outcomes representing differences in

recollection and interpretations (Figure 10).

Figure 10: Correlations between perceived uncertainty and key difference outcomes (n=60)



Correlation analysis found a significant negative relationship between perceptions of uncertainty and being non-Hispanic Caucasian such that those who were not Caucasian perceived greater certainty related to their variant result (P_c= -0.29 p=0.026). Furthermore, having children was found to be significantly negatively correlated with differences between recollection and thoughts of cancer risk such that those with children tended to under-interpret their risk to develop cancer compared to those without children (P_c = -0.321 p=0.014). No additional significant relationships were found among key variables and socio-demographic and other covariates measured in this study. Although this study is underpowered to detect correlations between key variables, those that are detected, are likely to persist following additional recruitment. With a larger sample size, we hope that further relationships between the key variables will be unveiled and can be tested in regression analyses.

DISCUSSION

Many clients who undergo testing for genetic cancer risk assessment (GCRA) receive variant of uncertain significance (VUS) result(s) that have no clinical utility. The purpose of this study was two-fold. First, this study sought to explore how individuals

who receive a VUS result in a cancer susceptibility gene perceive uncertainty related to their result. Additionally, this study sought to describe whether discrepancies between client recall and interpretation of genetic risk information are associated with their perceptions of uncertainty related to their VUS result. In the conceptual model (Figure 1), perceived uncertainty and personality traits are posited to contribute to meaning-based coping measured in this study as discrepancies between client's recall and interpretations, including thoughts and feeling, of uncertain genetic risk information.

Perceptions of Uncertainty

A VUS result is an inherently uncertain result. However, despite this fact most participants in this study perceived high levels of certainty related to personal aspects of their VUS result. The high level of perceived certainty persisted across all domains and was highest for the evaluative domain suggesting participants tended to perceived the greatest certainty about the accuracy and trustworthiness of their test result. However, this high level of certainty may not be warranted as recent reports have shown that it is a common occurrence for variants to have conflicting interpretations between genetic testing laboratories; 11% of 518 variants in one recent study (Balmana et al. 2016). One participant cited such a conflict in interpretation of results. It is also somewhat surprising that participants perceived high levels of clinical certainty related to their result. By definition the relationship between a VUS and health risks are unknown, which is why the National Clinical Cancer Network (NCCN) guidelines recommend against utilizing VUS results during GCRA or when making individualized management recommendations. Yet our findings suggest that clients perceive high certainty about how their results are related to their health, and how they and their doctor should use their

result to improve their health. This seems to suggest that clients may not appreciate how their GHP is (not) using their VUS result to inform their personalized risk assessment and management recommendations. Although in certain cases it may suggest that some health care providers are using VUS results to inform their risk counseling and management recommendations, which has been reported previously in studies of non-genetics health care providers (Plon et al., 2011, Cragun et al. 2016) and is supported by the one participant in this study that stated s/he had one doctor attribute meaning to their VUS result that had not been attributed by a GHP. Finally, participants reported high levels of certainty in the affective domain suggesting most felt certain about how they should emotionally respond to their result. This finding is interesting in the context of studies that have shown that some individuals receiving VUS results have greater psychological distress and worry compared to those receiving certain genetic test results (i.e. TN or PM) (van Dijk et al., 2006). Future studies could further elucidate how client's perceptions of affective uncertainty may or may not be related to their distress after receiving an uncertain result. Finally, despite the overall high perceptions of certainty, a few participants highlighted additional uncertainties that were not assessed by the PUGS. These uncertainties echoed uncertainties described in prior studies of individuals receiving VUS results including uncertainties about the meaning of their result for their future cancer risks, their family members' cancer risks, and when they should receive updated information about their variant or have additional genetic testing (Solomon et al. 2013). Although these qualitative results cannot be generalized to individuals with VUS results, the fact that they were identified in two independent samples suggest that genetics

health care providers should be aware and attending to these as potential uncertainties that may arise when counseling individuals with VUS results.

In this study personality traits were not related to overall perceptions of uncertainty as measured by the PUGS. However, those who were more ambiguity averse had lower perceptions of certainty about the trustworthiness and accuracy of their result, which is a relationship consistent with prior studies (Biesecker et al., 2016). Non-significance could suggest that these four personality traits do not contribute to how clients receiving a VUS result perceive personal uncertainties about their result. However, non-significance may also suggest that the small sample size and relative high ceiling for perceptions of certainty do not allow us to detect significant relationships. Studies with a larger sample population and greater diversity in perceptions of uncertainty would be better equipped to understand the actual relationships between personality traits and individual's perceptions of uncertainty related to their VUS result(s).

Another unique finding from this study was that clients perceived their genetic health care provider as having high certainty related to clinical and evaluative aspects of their genetic test result as well. This suggests that respondents perceived themselves as sharing what Han and colleagues describe as the 'locus of uncertainty'; whether uncertainty exists in the minds of the clients, the provider, or both. It makes sense that clients would perceive themselves as sharing their perceptions of certainty with their provider as patients often model their perceptions of uncertainties in part on their interpretation of what their health care provider communicated, often someone regarded as a trusted expert. However, it is curious how clients rated their certainty regarding their

test result as essentially the same between themselves and their GHP, but then expressed markedly disparate perceptions of their variant pathogenicity and cancer risks when compared to their GHP. This suggests that there are likely other factors that play a role in the re-interpretation process of uncertain genetic risk information than solely their perceptions of uncertainty related to their genetic test result. Following additional recruitment of participants, it will be intriguing whether this finding stands.

On the one hand, most participants in this study personally interpreted their result as being of uncertain significance while on the other they perceived few personal uncertainties about their result. While these viewpoints seem contradictory, they support Vos and colleagues' hypothesis that when faced with uncertain genetic test results individuals interpret the result with greater certainty as an adaptive way of coping with the uncertain information (Vos et al., 2008). In this way it is possible that participants perceived fewer personal uncertainties as a way of meaning based coping with the inherent uncertainty of their result. More research is needed to understand the consequences that may exist for clients perceiving a relatively high certainty about an uncertain genetic test result. However, if the goal of returning these results is to inform and educate clients about the uncertain nature of their result then data from this study suggests that message may be re-interpreted or lost in translation. Genetics health care providers have the opportunity during result disclosure to help clients explore their perceptions of certainty and/or uncertainty about their result, and help them to identify the potential consequences of holding these perceptions. Furthermore, they can use this exploration as a space to compare and contrast their own certainties and uncertainties

about their client's result, which may lead to a more empathic and shared understanding about their variant result.

Differences between recollection and interpretations

Results from this study suggest that many if not most individuals receiving a VUS result in a cancer susceptibility gene re-interpret the meaning of their variants' pathogenicity and their cancer risk perceptions as different from what they remember were communicated by their GHP. This is consistent with Vos and colleagues' findings among clients with a VUS result and expands it to those receiving a VUS in cancer susceptibility genes other than *BRCA1* and *BRCA2*. It is not novel, yet concerning, that some individuals in this study **recalled** that their GHP had classified their result as likely benign/benign or pathogenic. Moreover, half of participants **felt** that their variant was less or more pathogenic than what they recalled being communicated by their GHP, calling into question whether it is appropriate to return uncertain genetic test results to clients if a proportion will likely re-interpret their result's pathogenicity as meaning more or less than what they remember being communicated. This is especially important to consider in the context of Vos' research that suggested individual's interpretations of their variant result are better predictors of their risk perceptions, familial communication practices, and behavioral outcomes than their actually communicated result. More research is needed to replicate Vos' findings and strengthen the evidence for the consequences related to re-interpreting a VUS result as more or less pathogenic than their GHP.

Participants in this study perceived significantly higher cancer risk perceptions and hereditary likelihoods than their recollections, suggesting there may be a sense of 'false alarm' among this study population. Clients' tendency to over-interpret their

cancer risks and hereditary likelihood were not found to be related to their perceptions of uncertainty about their genetic test result, which may suggest that these perceptions are not associated with this phenomenon or that this study was not powered sufficiently to detect the actual relationship. We hypothesize that clients' tendency to over-interpret risk information may be related to several factors. The first factor being some aspect of receiving a VUS result since most participants reported that their genetic test result influenced their risk perceptions with ~30% of participants reporting that their genetic result highly influenced their interpretations. Another may be related to Vos and colleagues' hypothesis that clients reinterpret uncertain genetic information as having greater certainty as a way to cope with and manage their uncertainty. Although this seems discordant with the fact that most participants rated themselves as having high perceptions of certainty about their result, it is possible that the process of re-interpreting uncertain information as more certain occurs on a subconscious level that participants are unable to consciously report on. Furthermore, clients with a VUS may, and likely do, have a litany of other uncertainties (e.g. clinical, therapeutic, existential, etc.) that are more salient and play a larger role in the psychological process of re-interpretation of cancer risk information that were not measured in this study. Finally, we hypothesize that the tendency to re-interpret uncertain genetic information is influenced by factors related to GHP communication such as how much uncertainty is disclosed, how uncertainty is framed and how risks are presented.

Unlike Vos' studies, this study measured clients' thoughts and feelings as separate and distinct from each other. While client's thoughts and feelings were highly correlated in this study, participants' thoughts and feelings were often different from each other and

their feelings tended to show greater valence towards under and over-interpretation of their variant result and cancer risk information when compared to their thoughts. These differences suggest that GHPs should explore clients' thoughts and feelings about their VUS result and their cancer risk perceptions and can help normalize that their thoughts often are not the same as their feelings and the implications. Future research should investigate whether clients' feeling at greater or less risk than what they remember being communicated by their GHP may be a better predictor of psychological and behavioral outcomes than traditional cognitive perceptions of risk.

Clinical Implications

Findings from this study have implications for cancer health care providers who work with individuals with a VUS in a cancer susceptibility gene. This study contributes to the understanding of how clients with VUS results perceive certainties and uncertainties related to their result and how they form subjective interpretations regarding their variant's pathogenicity, cancer risks, and hereditary likelihoods. Data from this study suggests a disconnect exists between the inherent uncertainty of a VUS and individual's personal perceptions of uncertainty about the result. It is up to GHPs to help their patients appreciate the personal uncertainties that surround their VUS result and how their genetic test result is or is not clinically utilized. This can be accomplished through pretest discussions about potential personal uncertainties associated with VUS results, explicit explanations about uncertainties during result disclosure, and through exploring clients' perceived uncertainties about their result during and after disclosure. Furthermore, GHPs may make judgments of whether the potential harm of a client over-

interpreting the meaning of their result is less than the potential benefits of disclosing the VUS information to their patient.

In the context of disclosure, genetic health care providers such as genetic counselors can help clients make meaning of their results by engaging them in discussions about their personal thoughts and feelings regarding their result and their cancer risk perceptions. These conversations could then be leveraged as a means for GHPs to compare and contrast their own perspective with that of their clients. This is not to suggest that the ideal outcome would be for clients and GHPs to share the same perceptions. Rather GHPs could strive to help clients generate insight into how their thoughts and feelings may differ from their provider, and what the consequences of holding those perceptions are in their personal lives. In cases where clients' interpretations are related to negative outcomes such as unwarranted prophylactic surgery or psychological distress, their GHP can suggest resources to help them manage their uncertainty such as mindfulness based stress reduction or cognitive behavioral interventions. Our results also suggest that clients would be interested in having a clear follow-up plan for receiving updated information about their VUS results and the state of the genetic testing science. Collaborating with patients to put a follow-up plan in place during the disclosure session could be an additional way to reduce uncertainty surrounding a VUS result.

As indicated in the results, some socio-demographic variables were associated with perceptions of uncertainty and over-interpretation of cognitive cancer risk perceptions. This offers GHPs an opportunity to target interventions to those individuals who may be more susceptible to these tendencies. For example, it may be even more

helpful to spend time discussing and exploring personal uncertainties about VUS results with non-Caucasian clients who were more likely to perceive greater certainty related to their result in this study.

Study Limitations

While the results from this study can be used to inform clinical cancer genetic counseling practice, there are several important limitations. As mentioned previously, the small sample size for this study may prevent finding significant relationships between key variables. In addition, the use of a cross-sectional study design limits our ability to make inferences about how relationships between key variables change over time.

Other potential limitations may be related to the recruitment and the study population. Selection bias cannot be ruled out because it is possible that participants within the research registries that chose to participate may be different than those who chose not to participate. For instance, survey respondents may perceive higher certainty related to their genetic test result compared to non-respondents. The 16% response rate in this study was significantly lower than the 57% and 50% response rates reported in prior cross-sectional surveys among individuals enrolled in inherited cancer research registries (Culver et al., 2013; Vos et al., 2011). The lower response rate in this study may be attributed to several factors including; (1) participant concerns regarding privacy and confidentiality since this project was conducted by researchers at outside institutions (i.e. NIH and Johns Hopkins University); (2) additional burden since participants were required to review and provide a separate consent prior to completing the survey and; (3) the fact that prior studies did not stratify response rates by the registry participant's type of genetic test result (e.g. benign, VUS, pathogenic). Due to these limitations, it is

difficult to assess how our response rate compares to prior studies among individuals with a VUS recruited through inherited cancer research registries. Overall the study population was largely non-Hispanic Caucasian, female, married, and highly educated and therefore, may not be generalizable to the general U.S. population of individuals undergoing multi-gene panel testing for cancer susceptibility. However, these characteristics have been associated with cancer genetic testing historically (Balmana et al., 2016).

Finally, this study did not seek to compare differences between individual's recollections and interpretations and the objective information actually communicated by their GHP. Both recollections and interpretations may be biased due to selective hearing by the participant and heuristic information processing. Moreover, genetic counseling practices may be significantly different at academic centers than at community cancer centers or in medical settings outside of oncology where cancer genetic testing is increasingly offered. Therefore, system and provider level factors that could contribute to the variance in patients' recollections and interpretations of the genetic information outcomes may have been missed. Despite these limitations, this study was most interested in assessing interpretations of risk information because these are more deeply processed and connected with personal meaning. Identifying factors that influence how individuals reinterpret uncertain genetic information differently from their cognitive memory will be instrumental in developing interventions aimed at helping individuals make meaning of their uncertain genetic risk information rather than reducing their uncertainty.

Areas for future research

The purpose of this study was in part to examine the relationship between perceptions of uncertainty related to a variant result and discrepancies between recall and interpretations of uncertain genetic risk information. However, this study lacked the power to define these relationships at this time. Recruitment efforts will be continued to increase the sample size to allow for better interpretation of the relationships between key variables in this study. Future studies should include additional psychological and behavioral outcomes to better define what the consequences may be when an individual perceives him or herself and/or his or her families to be at greater risk for cancer as compared to their GHP. While this study was mainly interested in the client's perceptions of uncertainty and risk information, future analysis could measure the actual communication process between GHPs and clients when discussing VUS results in order to better understand provider level factors that may contribute to key variables in this study. The PUGS scale offers the ability to compare perceptions of uncertainty related to VUS results in various clinical populations including those outside of the cancer setting. The scale can also be applied to GHPs to assess their levels of perceived uncertainty related to their client's results, which can be contrasted to their clients' perceptions post disclosure. Finally, longitudinal studies are needed to better understand temporal relationships among the key variables and to understand the dynamic process of perceptions of uncertainty and re-interpretation of uncertain genetic information.

Conclusion

This cross-sectional study of individuals with a VUS result in a cancer susceptibility gene identified that most perceive a relatively high level of certainty about

personal aspects of their result. This calls into question whether clients properly appreciate the inherent uncertainties related to their result. Further, this study highlights many clients with a VUS result consciously think and feel differently about their genetic risk information than their memory of what was communicated by their GHP. Regardless of what most clients recall their GHP communicating, clients perceived themselves and their families to be at greater risk for cancer and attributed their genetic test result as influencing their perceptions. Based on these results, GHPs should critically consider whether the potential benefits of returning a VUS result are greater than the potential harms that may occur when their clients subjectively re-interpret the meaning of their variant result. If GHPs continue to return VUS results, this study has clinical implications for what GHPs should be addressing when discussing VUS result(s) at the time of disclosure and during follow-up care.

Appendix A: Recruitment Letter

[Participating Registry Logo]

Dear Participant,

You are being contacted because you are a part of the [Participating Hospital and Registry Title], which includes opportunities to be re-contacted for future research.

You are invited to participate in a study conducted by researchers at the National Institutes of Health, Johns Hopkins University and [Participating Hospital]. The purpose of this study is to learn more about the experiences of people who have undergone cancer genetic counseling and testing, and to learn what people think and feel about their genetic test result. Ultimately, we hope this research will help improve the cancer genetic counseling and testing experience.

The study involves filling out a survey, which we anticipate will take about 15 minutes to complete. The survey asks questions about your thoughts, feelings, and reactions to receiving your genetic test result. Individuals who join in this study will receive a $5 gift card as a token of our appreciation for your time.

You may participate in this study if:

1. You are 18 years or older
2. You can read and write in English
3. The interpretation of your genetic test result has <u>not</u> changed

The survey can be found online at [consent form/survey link]. If you prefer to complete a paper version of the survey, please contact Devon Bonner at [phone number] or [email] to receive the survey and a pre-addressed and stamped return envelope. Your privacy is important to us. Any contact information you give to the researchers will not be linked to your survey responses. Furthermore, only the researchers at [Participating Hospital] will have access to your private health information.

If you are willing to take part in this study, please read the information on the first page of the survey and check the box to show that you have read and voluntarily agreed to participate. If you agree to participate you will be asked to provide the authentication password listed below.

Your password is [unique password].

If you have any questions or concerns about this study please contact the researchers by phone or email. Thank you for your time and consideration. We look forward to learning from your responses.

Sincerely,

[Researchers signature and contact information]

Appendix B: Consent Document

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES
IRB #[IRB Number]: Understanding The Meaning Of Genetic Test Results For Cancer Susceptibility

I. **PURPOSE OF THIS RESEARCH STUDY**: You have been asked to participate in this research study because you are a part of the [Registry Protocol Title], which includes opportunities to be re-contacted for future research. The purpose of this study is to learn more about the experiences of people who have undergone cancer genetic counseling and testing, and to learn what people think and feel about their genetic test result. This study involves a one-time survey that takes approximately 15 minutes.

About ***240*** people will take part in this study.

II. **WHAT WILL BE DONE**: You will be invited to complete a survey:

- The survey will ask you about your genetic counseling and testing experience and how you think and feel about your genetic test result.
- Some of the questions will be multiple-choice while others will ask you to describe your thoughts and feelings in a few sentences.
- The survey will take approximately 15 minutes.

After completing the survey, you will be offered the opportunity to receive a $5.00 gift card, in recognition of your completion of the survey. If you agree to receive the $5 gift card, you will be asked to provide your name and contact address in a separate form that will not be linked to their survey responses or observed by the NIH researchers. Therefore, researchers at the NIH will not have access to identifiable information on survey respondents. The information you provide will only be used to send you the $5 gift card. Your information will be destroyed once the gift card is mailed to you.

If you want to remain anonymous, you should choose not to receive the $5 gift card or provide your information.

Whether or not you choose to receive the $5 gift card and provide your name and address will not affect your ability to participate on this study or your ability to receive treatment at this institution in the future.

If you choose to receive the $5 gift card and provide your name and address, the NIH researcher, Devon Bonner, will send you a $5 gift card. Your personal information will not be linked to your survey. We will not share your information with anyone outside the research team. The NIH researchers will analyze all study data anonymously and collectively. Your survey responses will not be placed in

your medical records. No reports from this study will include any information that could identify you.

III. **POSSIBLE BENEFITS**: You will not benefit from participation in this study. The information from this study may contribute to our understanding of cancer genetic testing and will be used to improve future patients' cancer genetic counseling and testing experiences.

IV. **POSSIBLE RISKS**: You may become tired from the amount of time needed to fill out the survey. It is possible that the content of the questions asked could upset you or make you uncomfortable. You can stop answering any questions at any time. If you feel upset by the survey you can contact the researchers listed below. You may also choose to contact your genetic counselor or doctor.

V. **ALTERNATIVES TO PARTICIPATION**: Your alternative is to choose not to participate in this study. Choosing not to participate will not interfere with any relationship with City of Hope.

VI. **CONFIDENTIALITY OF INFORMATION**: Any information learned from this study in which you might be identified will be confidential and disclosed only with your permission. Every effort will be made to keep any information collected about you confidential. If you choose to receive the $5 gift card and provide your name and contact address, it is impossible to guarantee that information about you will not be mistakenly released. If, despite our best efforts, identifying information about you is released, it could negatively impact you or your family members. This risk is small.

However, you allow the researchers to make your information available to Institutional Review Board (IRB) Office, the Cancer Protocol Review and Monitoring Committee (CPRMC), the Office for Human Research Protections (OHRP), the National Cancer Institute (NCI), and other regulatory agencies as required by law.

VII. **OFFER TO ANSWER QUESTIONS**: If you have any further questions or concerns about this study, you can contact the principal investigator, [Collaborating PI] at [PI phone number] or the research genetic counselor, [Genetic counselor name and phone number]. You may also contact the NIH researcher, Devon Bonner, at [Phone number].

VIII. **SPONSOR OF THIS RESEARCH**: The National Human Genome Research Institute Intramural Research Program at the National Institute of Health (NIH) is the sponsor of this research study.

IX. **COST TO THE RESEARCH PARTICIPANT FOR PARTICIPATION**: Neither you nor your insurance carrier will be charged for your participation in this study.

X. **FINANCIAL COMPENSATION**: You will be offered a $5 gift card after completing the survey. You will be able to choose to receive your gift card by email or mail. Any contact information you provide will be destroyed after the gift card is sent. You are not required to receive a gift card to take part in the study.

XI. **VOLUNTARY PARTICIPATION WITH RIGHT OF REFUSAL**: You have been informed that your participation in this research study is voluntary. You are free to withdraw your consent for participation in this study without any loss of benefits, penalty, or interference with [Collaborating hospital].

XII. **IRB REVIEW AND IMPARTIAL THIRD PARTY**: This study has been reviewed and approved by the Institutional Review Board (IRB). A representative of that Board, from the Office of Human Research Subjects Protection, is available to discuss the review process or your rights as a research subject. The telephone number of the Office of Human Research Subjects Protection is (626) 256-HOPE (4673) ext. 62700.

XIII. **AGREEMENT TO PARTICIPATION:** By completing the survey you agree to participate in this research study.

Appendix C: Survey Instrument

Instructions: This survey should take you about 15 minutes to complete. Any responses you give will be anonymous and will not be linked to your private health information. The questions address your thoughts, feelings, and experiences with genetic testing. Some items are quite similar, but your thoughts and feelings may not always be the same. There are no right or wrong answers.

Section A
This section asks questions about your perceptions of uncertainty related to your genetic test result. There are no right or wrong answers.

1. In the table below, rate how uncertain or certain you are about the following aspects of your genetic test results.

	Very uncertain	Somewhat uncertain	Neither certain nor uncertain	Somewhat certain	Very certain
What my test results may mean for my health.	❒	❒	❒	❒	❒
What actions I need to take based on my test results.	❒	❒	❒	❒	❒
How my doctor may use my results to improve my health.	❒	❒	❒	❒	❒
Whether to be worried or concerned about my test results.	❒	❒	❒	❒	❒
Whether to be alarmed about my test results.	❒	❒	❒	❒	❒
Whether my test results will disrupt my life.	❒	❒	❒	❒	❒
Whether I can trust my test results.	❒	❒	❒	❒	❒
Whether my test results are accurate.	❒	❒	❒	❒	❒

2. Please describe anything else you are unsure about regarding your genetic test result. Write as little or as much as you want.

3. In what ways do you see any positive aspects (**good things**) about any of the uncertainties surrounding your test results? Write as little or as much as you want.

4. In what ways do you see any negative aspects (**bad things**) about any of the uncertainties surrounding your test results? Write as little or as much as you want.

5. Generally, how are you feeling about the uncertainties related to your genetic test result? Please describe your feelings below in a few sentences.

6. We are also interested in your impressions of <u>your genetic counselor or doctor's uncertainty</u> about your test results. Please rate how uncertain or certain you think s/he is about your genetic test results.

	Very uncertain	Somewhat uncertain	Neither certain nor uncertain	Somewhat certain	Very certain
What my test results may mean for my health.	❒	❒	❒	❒	❒
What actions I need to take based on my test results.	❒	❒	❒	❒	❒
How they may use my results to improve my health.	❒	❒	❒	❒	❒
Whether they can trust my test results.	❒	❒	❒	❒	❒
Whether my test results are accurate.	❒	❒	❒	❒	❒

Section B

Moving on from your own thoughts and feelings, we are interested in what you *remember* talking about with your genetic counselor or doctor. Please do not worry about whether what you remember is correct.

7. How many variants (genetic changes) did your genetic counselor or doctor tell you were identified by your genetic test? _____

8. If you learned of more than one variant, please think about the one that is most important or that you feel may mean the most for you. How did your genetic counselor or doctor classify this variant? Note that 'benign' means that a variant is present but the gene still works properly while 'pathogenic' means the variant is damaging (meaning the gene does not work properly). 'Uncertain significance' means that a variant is present but it is unknown whether the gene works properly or not.

Benign	Likely benign	Uncertain Significance	Likely pathogenic	Pathogenic

9. What is your risk to develop cancer in the future according to your genetic counselor or doctor?

Extremely unlikely	Very unlikely	Somewhat unlikely	Unsure	Somewhat likely	Very likely	Extremely likely

10. According to your genetic counselor or doctor what is the chance that cancer is passed down from generation to generation in your family?

Extremely unlikely	Very unlikely	Somewhat unlikely	Unsure	Somewhat likely	Very likely	Extremely likely

Section C

Please share your thoughts and feelings about your genetic test result, regardless of what any other person thinks or feels. There are no right or wrong answers.

11. Please think about the same variant you kept in mind for the prior questions when completing the statements in the table below. Note that 'benign' means that a variant is present but the gene still works properly while 'pathogenic' means the variant is damaging (meaning the gene does not work properly). 'Uncertain significance' means that a variant is present but it is unknown whether the gene works properly or not.

	Benign	Likely benign	Uncertain significance	Likely pathogenic	Pathogenic
I *think* my variant is…	❒	❒	❒	❒	❒
I *feel* my variant is…	❒	❒	❒	❒	❒

12. In the table below, rate how likely you believe each statement is for you.

	Extremely unlikely	Very unlikely	Somewhat unlikely	Unsure	Somewhat likely	Very likely	Extremely likely
I *think* that my risk to develop cancer in the future is…	❒	❒	❒	❒	❒	❒	❒
I *feel* my risk to develop cancer in the future is…	❒	❒	❒	❒	❒	❒	❒
I *think* the chance that cancer is passed down from generation to generation in my family is…	❒	❒	❒	❒	❒	❒	❒
I *feel* the chance that cancer is passed down from generation to generation in my family is…	❒	❒	❒	❒	❒	❒	❒

13. In this next table, please rate how much your genetic test result has influenced each of your beliefs stated in the table above.

	Not at all	Not very much	A little bit	Unsure	Somewhat	Very much	Extremely
How much are your *thoughts* about your risk to develop cancer in the future influenced by your genetic test result?	❒	❒	❒	❒	❒	❒	❒
How much are your *feelings* about your risk to develop cancer in the future influenced by your genetic test result?	❒	❒	❒	❒	❒	❒	❒

	Not at all	Not very much	A little bit	Unsure	Somewhat	Very much	Extremely
How much are your *thoughts* about the chance that cancer is passed down from generation to generation in your family influenced by your genetic test result?	❒	❒	❒	❒	❒	❒	❒
How much are your *feelings* about the chance that cancer is passed down from generation to generation in your family influenced by your genetic test result?	❒	❒	❒	❒	❒	❒	❒

14. Please write what types of cancer you *think* you are at risk of developing.

15. Please write what types of cancer you *feel* that you are at risk of developing?

16. In what ways (if any) has your genetic test result changed your perception of cancers you are at risk for? Write as little or as much as you want.

17. Please write the types of cancer you *think* may be passed down in your family.

18. Please write what types of cancer you *feel* may be passed down in your family.

19. In what ways (if any) has your genetic test result influenced your perception of the chance that cancer is passed down from generation to generation in your family? Write as little or as much as you want.

_____

_____

Section D

20. Please rate how well the following statements describe you. Rate each item on a scale from 1 (Not at all characteristic of me) to 5(Entirely characteristic of me).

	Not at all characteristic of me 1	Somewhat 2	Unsure 3	Very 4	Entirely characteristic of me 5
It really disturbs me when I am unable to follow another person's train of thought.	❒	❒	❒	❒	❒
If I am uncertain about the responsibilities involved in a particular task, I get very anxious.	❒	❒	❒	❒	❒
Before an important task I must know how long it will take.	❒	❒	❒	❒	❒
I don't like to work on a problem unless there is a possibility of getting a clear-cut and unambiguous answer.	❒	❒	❒	❒	❒
The best part of working on a jigsaw puzzle is putting in that last piece.	❒	❒	❒	❒	❒
I am often uncomfortable with people unless I feel that I can understand their behavior.	❒	❒	❒	❒	❒
A good task is one in which what is to be done and how it is to be done are always clear.	❒	❒	❒	❒	❒

21. Please rate how strongly you agree with each statement as it describes you.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
In uncertain times, I usually expect the best.	❒	❒	❒	❒	❒
It's easy for me to relax.	❒	❒	❒	❒	❒
If something can go wrong for me, it will.	❒	❒	❒	❒	❒
I'm always optimistic about my future.	❒	❒	❒	❒	❒
I enjoy my friends a lot.	❒	❒	❒	❒	❒
It's important for me to keep busy.	❒	❒	❒	❒	❒
I hardly ever expect things to go my way.	❒	❒	❒	❒	❒
I don't get upset too easily.	❒	❒	❒	❒	❒
I rarely count on good things happening to me.	❒	❒	❒	❒	❒
Overall, I expect more good things to happen to me than bad.	❒	❒	❒	❒	❒

22. Please rate how strongly you agree with each statement as it describes you.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Conflicting expert opinions about a medical test or treatment would lower my trust in the experts.	❒	❒	❒	❒	❒
I would **not** have confidence in a medical test or treatment if experts had conflicting opinions about it.	❒	❒	❒	❒	❒
Conflicting expert opinions about a medical test or treatment would make me upset.	❒	❒	❒	❒	❒
I would **not** be afraid of trying a medical test or treatment even if experts had conflicting opinions about them.	❒	❒	❒	❒	❒
If experts had conflicting opinions about a medical test or treatment, I would still be willing to try it.	❒	❒	❒	❒	❒
I would avoid making a decision about a medical test or treatment if experts had conflicting opinions about it.	❒	❒	❒	❒	❒

23. Please rate the degree to which the following statements are true about you.

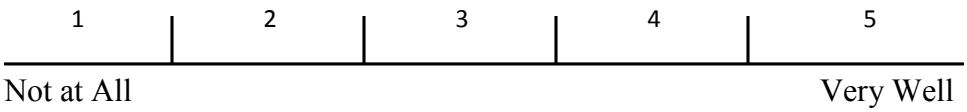
	Never True	Seldom True	Sometimes True	Often True	Always True
I am able to adapt to change.	❒	❒	❒	❒	❒
I can deal with whatever comes.	❒	❒	❒	❒	❒
I see the humorous side of things.	❒	❒	❒	❒	❒
Coping with stress makes me stronger.	❒	❒	❒	❒	❒
I tend to bounce back after illness, injury or hardship.	❒	❒	❒	❒	❒
I can achieve my goals.	❒	❒	❒	❒	❒
Under pressure, I focus and think clearly.	❒	❒	❒	❒	❒
I am not easily discouraged by failure.	❒	❒	❒	❒	❒
I think of myself as strong person.	❒	❒	❒	❒	❒
I can handle unpleasant feelings.	❒	❒	❒	❒	❒

Section E

24. To your knowledge, are you the first person in your family to have cancer genetic testing?
    - ❒ Yes
    - ❒ No

25. Before receiving your genetic test result, had you taken into account the possibility of receiving an uncertain result?
    - ❒ Yes
    - ❒ No

26. How confident do you feel that you understand the genetic test result?



27. Please rate how strongly you agree or disagree with each statement about your decision to have genetic testing.

	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
It was the right decision	❒	❒	❒	❒	❒
I regret the choice that was made	❒	❒	❒	❒	❒
I would go for the same choice if I had to do it over again	❒	❒	❒	❒	❒
The choice did me a lot of harm	❒	❒	❒	❒	❒
The decision was a wise one	❒	❒	❒	❒	❒

28. Did you receive a letter or test report that summarized the information discussed when you received your genetic test result?

❒ Yes→ If yes, continue to question 29
❒ No

29. During the course of taking this survey, did you review this letter or report?

❒ Yes
❒ No

Appendix D: List of genes and associated cancers

Gene	Associated Neoplasia	Citations
APC	Colon carcinoma Desmoid tumor Adrenal carcinoma Thyroid papillary carcinoma Gastric adenocarcinoma Medulloblastoma Hepatoblastoma Small intestine carcinoid Astrocytoma Osteoma	OMIM: 175100, 135290 NCCN guidelines: v.2.2016
ATM	Breast cancer Lymphoma (bi) Leukemia (bi)	OMIM: 208900 NCCN guidelines: v.2.2016
BRCA1	Breast Cancer Ovarian, Fallopian Tube, and Peritoneal Cancer Prostate Cancer	OMIM: 604370, 614320 NCCN guidelines: v.2.2016
BRCA2	Breast Cancer Ovarian, Fallopian Tube, and Peritoneal Cancer Prostate Cancer Pancreatic Cancer Melanoma Wilms Tumor (bi) Glioblastoma (bi) Medulloblastoma (bi) Leukemia (bi)	OMIM: 605724, 194070, 612555, 613347 NCCN guidelines: v.2.2016
BRIP1	Ovarian, Fallopian Tube, and Peritoneal Cancer Leukemia (bi)	OMIM: 605882, 609054 NCCN guidelines: v.2.2016
CHECK2	Breast Cancer Colorectal Cancer Prostate Cancer Stomach Cancer Sarcoma Renal Cancer	OMIM: 604373 NCCN guidelines: v.2.2016
CDH1	Lobular Breast Cancer Diffuse Gastric Cancer	OMIM: 192090 NCCN guidelines: v.2.2016
DIS3L2	Wilms Tumors	OMIM: 614184

	Renal Hamartomas (bi)	
MLH1	Colorectal Cancer Ovarian Cancer Endometrial Cancer Gastric Cancer Hepatobillary Tract Cancer Urinary Tract Cancer Small Bowel Cancer Brain Cancer Sebaceous Neoplasms Pancreatic Cancer Ependymoma (bi) Glioblastoma (bi) Oligodendroglioma (bi) Neuroblastoma (bi) Astrocytoma (bi) Medulloblastoma (bi) Colonic adenocarcinoma (bi) Leukemia (bi) Lymphoma (bi) Rhabdomyosarcoma (bi)	OMIM: 120436, 609310, 276300 NCCN guidelines: v.2.2016
MSH2	Colorectal Cancer Ovarian Cancer Endometrial Cancer Gastric Cancer Hepatobillary Tract Cancer Urinary Tract Cancer Small Bowel Cancer Brain Cancer Sebaceous Neoplasms Pancreatic Cancer Ependymoma (bi) Glioblastoma (bi) Oligodendroglioma (bi) Neuroblastoma (bi) Astrocytoma (bi) Medulloblastoma (bi) Colonic adenocarcinoma (bi) Leukemia (bi) Lymphoma (bi) Rhabdomyosarcoma (bi)	OMIM: 609309, 609310, 276300 NCCN guidelines: v.2.2016
MSH6	Colorectal Cancer Ovarian Cancer Endometrial Cancer Gastric Cancer	OMIM: 600678, 614350, 276300 NCCN guidelines: v.2.2016

	Ependymoma (bi) Glioblastoma (bi) Oligodendroglioma (bi) Neuroblastoma (bi) Astrocytoma (bi) Medulloblastoma (bi) Colonic adenocarcinoma (bi) Leukemia (bi) Lymphoma (bi) Rhabdomyosarcoma (bi)	
MUTYH	Colorectal Cancer (bi) Duodenal Cancer	OMIM: 604933 NCCN guidelines: v.2.2016
NBN	Breast Cancer Ovarian Cancer Lymphoma (bi) Gliomas (bi) Medulloblastoma (bi) Rhabdomyosarcoma (bi)	OMIM: 602667, 251260 NCCN guidelines: v.2.2016
NF1	Breast Cancer Optic glioma Malignant peripheral nerve sheath tumors Meningioma Hypothalamic tumor Neurofibrosarcoma Rhabdomyosarcoma Duodenal carcinoid Somatostatinoma Parathyroid adenoma Pheochromocytoma Pilocytic astrocytoma	OMIM: 162200 NCCN Guidelines: v 2.2016
PALB2	Breast Cancer Pancreatic Cancer Ovarian Cancer Wilms Tumor (bi) Glioblastoma (bi) Medulloblastoma (bi) Leukemia (bi)	OMIM: 610355, 610832 NCCN guidelines: v.2.2016
PMS2	Colorectal Cancer Endometrial Cancer Ependymoma (bi) Glioblastoma (bi) Oligodendroglioma (bi) Neuroblastoma (bi) Astrocytoma (bi)	OMIM: 600259, 614337, 276300 NCCN guidelines: v.2.2016

	Medulloblastoma (bi) Colonic adenocarcinoma (bi) Leukemia (bi) Lymphoma (bi) Rhabdomyosarcoma (bi)	
POLD1	Colorectal Cancer Uterine Cancer	OMIM: 174761, 612591
PTEN	Breast Cancer Thyroid Cancer (follicular) Uterine Cancer Renal Cancer Colorectal Cancer Melanoma Hamartomas or ganglioneuromas (GI)	OMIM: 601728 NCCN Guidelines: v 2.2016
RAD50	Ovarian Cancer Breast Cancer	OMIM: 604040
RAD51C	Ovarian Cancer	OMIM: 602774 NCCN Guidelines: v 2.2016
RAD51D	Ovarian Cancer	OMIM: 602954 NCCN Guidelines: v 2.2016
SDHC	Paragangliomas Pheochromocytomas Gastrointestinal stromal tumors Renal cancer	OMIM: 602413, 606764
STK11	Breast Cancer Colon Cancer Gastric Cancer Small Intestine Pancreatic Cancer Ovarian Cancer (sex cord tumor w/ annular tubules) Cervical Cancer Uterine Cancer Sertoli cell testicular cancer Lung Cancer	OMIM: 602216 NCCN Guidelines: v 2.2016
SMAD4	Colorectal Cancer Gastric Cancer Small Intestine Cancer Pancreatic Cancer	OMIM: 600993 NCCN Guidelines: v 2.2016
TSC2	Renal carcinoma Neuroendocrine tumors Ependymoma Giant cell astrocytoma	OMIM: 191092, 613254

	Chordoma Benign tumors of the eye, heart, and lungs	
VHL	Renal Cancer Pheochromocytomas Neuroendocrime Tumors of the Pancreas Hemangioblastoma Paraganglioma	OMIM: 608537, 193300

Bi= biallelic mutation carriers
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CURRICULUM VITAE

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Education:

- University of South Florida: (Tampa, FL), Bachelor of Art, Dec 2011 (Psychology)
- Johns Hopkins University: Bloomberg School of Public Health (Baltimore, MD), Master of Science, Anticipated Graduation Date: January 27, 2017
  - Thesis: Understanding how clients make meaning of their variants of uncertain significance in the age of multi-gene panel testing for cancer susceptibility.
- National Human Genome Research Institute, Intramural Research Training Award, Dr. Barbara Biesecker, Aug 2014- Jan 2017

Licensure and Certification:

- CITI Training Initiative Biomedical Research Curriculum, June 2016

Hospital Appointments

- Research Coordinator, Department of Cancer Epidemiology, Moffitt Cancer Center, Aug 2010-Aug 2014

Professional Organizations:

- American Association of Cancer Research (AACR), Member since 2012
- National Society of Genetic Counselors (NSGC), Member since 2014

Professional Activities:

- Genetic Counseling Training:
  - GeneDx, Inc. (Gaithersburg, MD) Oct 2014-Dec 2014

- Howard County Hospital, Maternal and Fetal Medicine, (Columbia, MD) Jan 2015- May 2015
- City of Hope, Division of Clinical Cancer Genetics, (Duarte, CA) June 2015-July 2015
- Children's National Medical Center, Pediatric Genetics Clinic, (Washington D.C.) Sep 2015-Dec 2015
- Children's National Medical Center, Pediatric Oncology Clinic, (Washington D.C.) Oct 2015-Dec 2015
- National Human Genome Research Institute, NIH (Bethesda, MD) Mar 2016-Aug 2016
- National Institute of Neurologic Disorders and Stroke, NIH (Bethesda, MD) Mar 2016-May 2016
- Kennedy Krieger Institute, Neurology and Neurogenetics Clinic (Baltimore, MD) Sep 2016-Oct 2016
- John Hopkins Hospital, Center for Inherited Heart Diseases, (Baltimore, MD) Oct 2016-Dec 2016

Publications and Presentations:

Peer-Reviewed Publications:

1. Pal T, **Bonner D**, Kim J, Monteiro AN, Kessler L, Royer R, Narod SA, Vadaparampil ST. Early onset breast cancer in a registry-based sample of African-american women: BRCA mutation prevalence, and other personal and system-level clinical characteristics. *Breast J*. 19(2):189-192. 2013 Sep
2. Pal T, **Bonner D**, Cragun D, Johnson S, Akbari M, Servais L, Narod S, Vadaparampil S. BRCA sequencing and large rearrangement testing in young Black women with breast cancer. *J Community Genet*. 5(2):157-165. 2014 Apr
3. Cragun D, **Bonner D**, Kim J, Akbari MR, Narod SA, Gomez-Fuego A, Garcia JD, Vadaparampil ST, Pal T. Factors associated with genetic counseling and BRCA testing in a population-based sample of young Black women with breast cancer. *Breast Cancer Res Treat*. 2015 May
4. Pal T, **Bonner D**, Cragun D, Monteiro AN, Phelan C, Servais L, Kim J, Narod SA, Akbari MR, Vadaparampil ST. A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. *Cancer*. 121(23):4173-4180. 2015 Dec
5. **Bonner D**, Cragun D, Reynolds M, Vadaparampil ST, Pal T. Recruitment of a Population-Based Sample of Young Black Women with Breast Cancer through a State Cancer Registry. *Breast J*. 22(2):166-172. *2016 Mar*

Other Publications:

1. **Bonner D**, Vadaparmpil ST, Malo T, Pal T. A closer look at risk perception among Black women at increased risk of hereditary breast and ovarian cancer. Thesis, University of South Florida, 2011.

2. **Bonner D**, Cragun D, Solomon I, Tibben A, Biesecker BB. Understanding how clients make meaning of their variants of uncertain significance in the age of multi-gene panel testing for cancer susceptibility. Thesis, Johns Hopkins University, 2017.

Peer-Reviewed Presentations at Scientific Meetings:

1. The Use of Academic-Community Partnerships in Participant Accrual to an Inherited Cancer Registry. Presented as a poster to the National Conference of Undergraduate Research, April 2011, Ithica, New York.
2. Risk Perception among Black Women at Increased Risk for Hereditary Breast and Ovarian Cancer One Year after Receiving BRCA Results. Presented as a poster to the Moffitt Scientific Symposium, 2012, Tampa, FL.
3. The utility of a state-wide cancer registry in recruiting a clinically representative population-based sample of young Black women diagnosed with early-onset breast cancer. Presented as a Poster at the Fifth AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, October 2012, San Diego, CA.
4. Access to Genetic Counseling and BRCA Testing Among a Population-Based Sample of Black Women with Early-Onset Breast Cancer. Presented as a poster presentation at the Thirty-third NSGC Annual Education Conference, September 2014, New Orleans, LA.
5. A population-based sample of breast cancer survivors who accessed genetic counseling and *BRCA* testing recalled greater adherence to cancer genetic counseling practice guidelines when a genetic healthcare provider was involved. Accepted for poster presentation at the Thirty-fourth NSGC Annual Education Conference, October 2015, Pittsburg, PA.
6. Understanding how clients make meaning of their variants of uncertain significance in the age of multi-gene panel testing for cancer susceptibility. Accepted for poster presentation at the NHGRI Scientific Symposium, November 2016, Bethesda, MD.